

Treatment of Demyelinating Disorders
Pharmaceutical compositions and their uses

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A1

The present invention relates *inter alia* to the treatment of demyelinating disorders.

5 The majority of excitatory synaptic responses in mammalian CNS are elicited by amino acids such as L-glutamate or L-aspartate and are mediated by four different receptor subtypes. Three of these receptors are coupled to ionophores and are known as the N-methyl-D-aspartate (NMDA), the AMPA α -amino-3-hydroxy-5-methyl-4-isoxazole-propionate), and the kainate receptors. Typically these receptors will be in
10 the form of a receptor complex including for example glutamate and/or agonist binding site(s), modulatory site(s) and an ion channel, and possibly also including other moieties interacting with the function of the channel. The fourth receptor subtype is linked to phosphoinositol metabolism and is known as the metabotropic glutamate receptor.

15 The NMDA receptor is coupled to high conductance channels permeable to Na^+ , K^+ , and Ca^{2+} (McBain CJ, Mayer M (1994): N-Methyl-D-aspartic acid receptor structure and function, *Physiol. Rev.*, 74:723-760). It is modulated by glycine (coagonist) and polyamines (positive modulator) and is blocked in a use- and voltage dependent
20 manner by Mg^{2+} . The functional NMDA receptor is thought to be formed as a pentameric subunit assembly consisting of subunit selection from NR1 (eight isoforms) and NR2 (four isoforms) families (Hollmann M, Heinemann S (1994): Cloned glutamate receptors, *Annu. Rev. Neurosci.* 17:31-108). The type of subunits forming the NMDA channel determine its biophysical properties and physiological
25 function (Schöpfer R, Monyer H, Sommer B, Wisden W, Sprengel R, Kuner T, Lomeli H, Herb A, Kohler M, Burnashev N (1994): Molecular biology of glutamate receptors, *Prog. Neurobiol.* 42:353-357). The AMPA and kainate receptors are permeable to Na^+ and K^+ (Hollmann and Heinemann, 1994 [*supra*]). AMPA receptor-dependent ion channel is formed from four different subunits designated as GluR1 to

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GluR4 (in two alternative splice variants - flip and flop) in a tetrameric subunit assembly (Hollmann and Heinemann, 1994 [supra]; Rosenmund C, Stern-Bach Y, Stevens C (1998): The tetrameric structure of a glutamate receptor channel, Science 280:1596-1599). Pharmacological properties of AMPA receptor-dependent ion channels are determined by the selection of subunits. Channel assemblies lacking GluR2 subunits are permeable to Ca^{2+} in addition to Na^{+} - and K^{+} -permeability (Hollmann and Heinemann, 1994 [supra]). *In situ* hybridization has revealed different expression of glutamate receptor subunits throughout the brain and during development (Monyer H, Burnashev N, Laurie DJ, Sakmann B, Seeburg P (1994): Developmental and regional expression in the rat brain and functional properties of four NMDA receptors, Neuron 12:529-540).

Kainate receptors represent the third type of ionotropic glutamate receptors (E. A. Barnard, Ionotropic glutamate receptors: new types and new concepts. Trends Pharmacol. Sci. 18: 141-148, 1997). The kainate receptors are formed heterometrically by GluR5-7 and KA1-2 types of subunits (Y. Paas, The macro- and microarchitectures of the ligand-binding domain of glutamate receptors. Trends in Neurosci. 21, 117-125, 1998). By being activated (opened) and desensitized (closed) by glutamate, kainate receptors modulate a passive flow of Na^{+} , K^{+} and to varying degree, Ca^{2+} ions across the cell membrane. As such kainate receptors mediate fast synaptic transmission in the nervous system and are involved in plasticity, transmission of sensory signals and in development (E. A. Barnard, *ibid*). Furthermore, kainate receptors are unevenly distributed in the brain and spinal cord of rodents and primates (J. M. Henley, Trends Pharmacol. Sci. 15, 182-190, 1994). Dysfunction of kainate receptors may contribute to pathogenesis of variety of neurological and psychiatric disorders (B. Meldrum and J. Garthwaite, Trends Pharmacol. Sci. 11, 379-387, 1990).

In contrast to the well documented role of glutamate in the pathogenesis of neuronal degeneration resulting from hypoxia/ischemia, hypoglycemia, convulsions and head or spinal cord trauma, no clear link has been established between glutamate-mediated cell death and demyelinating disorders. Many demyelinating disorders have previously
5 been resistant to therapy. Furthermore, until recently, the treatment of human demyelinating disorders has relied exclusively on the use of immunosuppressive agents such as corticosteroids and cyclophosphamide, which although providing limited benefit to patients, can be associated with potentially serious side effects. The introduction of interferon preparations has provided efficacy in the treatment of certain
10 demyelinating disorders (e.g. multiple sclerosis). However, as benefits are apparent in only a portion of the subgroup of patients classified as suitable for treatment, then management of the disease is still insufficient with such preparations.

The present inventors have now provided evidence in support of the involvement of
15 glutamate in the pathogenesis of demyelinating disorders. They have established a link between neuronal demyelination and glutamate-mediated cell death using accepted animal models of a demyelinating disorder.

The present invention represents a major advance over prior art methods in the
20 treatment of demyelinating disorders.

According to one aspect of the present invention, there is provided the use of an inhibitor of the interaction of glutamate with the AMPA and/or kainate receptor complex in the manufacture of a medicament for treating a demyelinating disorder.
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The term "inhibitor of the interaction of glutamate with the AMPA and/or kainate receptor complex" is used herein to include moieties that bind to the AMPA and/or kainate receptor or to glutamate so as to prevent or reduce the binding of glutamate to its binding site on the AMPA and/or kainate receptor. Such moieties may bind in a
30 competitive or non-competitive manner. They are referred to herein as "antagonists"

of the binding of glutamate to the AMPA and/or kainate receptor. A skilled person is able to identify substances that may be useful as antagonists of the present invention by binding studies. For example, the AMPA and/or kainate receptor, a part thereof including said glutamate binding site, or a glutamate molecule can be used to screen for substances that bind thereto, preferably in a highly specific manner. Such binding studies can be part of a screening program for identifying or designing potential therapeutic agents. More specifically, a skilled person could identify inhibitors of the interaction of glutamate with the AMPA and/or kainate receptor complex using, for example, *in vitro* calcium ion-increase assays or the whole cell configuration of the patch clamp technique. Cells expressing the AMPA receptor complex could be obtained, for example, from dissociated cortical or hippocampal cells. Cells expressing the kainate receptor complex could be obtained, for example, from dissociated dorsal root ganglion cells. Inhibition of the interaction of agonists, for example glutamate, AMPA or kainate, of the AMPA and/or kainate receptor complex could be assayed by incubation of the agonist with and without antagonist and the cellular response (eg change in intra-cellular calcium ion concentration or change in membrane potential) measured.

The term "inhibitor of the interaction of glutamate with the AMPA and/or kainate receptor complex" also includes moieties that prevent a signal being transmitted that would otherwise occur when glutamate binds to the AMPA and/or kainate receptor. Preferred such moieties are AMPA and/or kainate receptor channel blockers. The term "AMPA and/or kainate receptor channel blocker" is used herein to refer to moieties that reduce the permeability of ion channels associated with the AMPA and/or kainate receptor *in vivo* (preferably to Na^+ , K^+ and/or Ca^{2+} ions).

Various antagonists and AMPA receptor channel blockers that are within the scope of the present invention will now be described in greater detail:

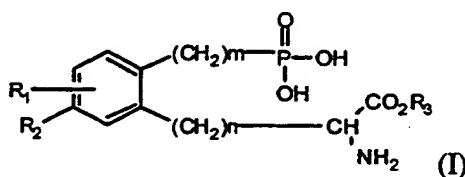
Antagonists

The antagonists of the present invention include L-glutamate derivatives such as e.g. L-glutamic acid diethylester, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate derivatives such e.g., α -amino-3-hydroxy-5-tert-buthyl-4-isoxazolepropionic acid, quinoline, quinoxaline, quinoxalinedione, quinazolinone, phenylpyridazino-indole-1,4-dione, indeno-pyrazinone, indeno-pyrazine-carboxylic acid, indolo-pyrazinone, imidazo-pyrazinone, amino-phenyl-acetic acid, benzothiadiazine, 4-hydroxypyrrolone, 4-hydroxy-pyrrolo-pyridazinone, quinolone, amino alkanoic acid, isatin, nitroquinolone, phenyl-azolophthalazine, amino- or desamino- 2,3-benzodiazepine, 2,3-benzodiazepin-4-one, β -carboline-3-carboxylic acid, alkoxy-phenyl-benzodiazepine, acetyl-aminophenyl-dihydro-methyl-dioxolo-benzodiazepine, oxadiazol, isatinoxime, decahydroisoquinoline, and sulphamate.

Further substances that may be useful as antagonists are listed below:

List of Antagonists

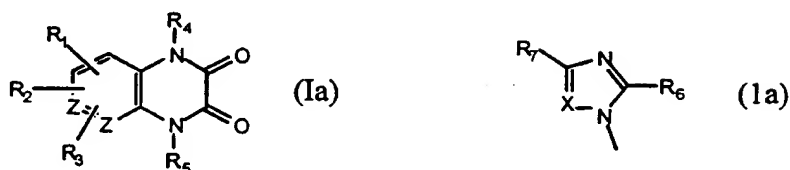
(1) ω -[2-(Phosphonoalkyl)phenyl]-2-aminoalkanoic acids (I) in WO 93-05772 as shown below:



ω -[2-(Phosphonoalkyl)phenyl]-2-aminoalkanoic acids represented by formula (I), wherein n and m independently are 0, 1, 2 or 3; R^1 is selected from the group consisting of hydrogen and R^2 ; R^2 is selected from the group consisting of hydrogen, halogen, halomethyl, nitro, amino, alkoxy, hydroxyl, hydroxymethyl, C_1 to C_6 lower alkyl, C_7 to C_{12} higher alkyl, aryl and aralkyl, wherein if R^2 is hydrogen, R^1 is not hydrogen; R^3 is selected from the group consisting of hydrogen and C_1 to C_6 lower

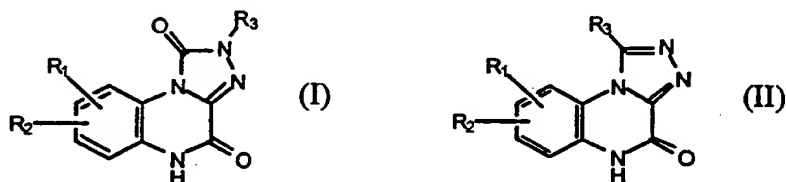
alkyl; the stereoisomers thereof in their resolved or racemic form, and pharmaceutically acceptable salts thereof.

- 5 (2) Fused pyperazine derivatives in WO 92-07847 as shown below:



- 10 A pyperazine derivative represented by general formula (Ia) wherein Z represents C or N, provided that two Zs are not N atoms at the same time; R^1 represents (1a) wherein X represents N or R^8C , R^6 represents H or alkyl, and R^7 and R^8 represent each H, alkyl, nitro or phenyl, or alternatively R^7 and R^8 are combined together to represent butadienylene or 1,4-butylene; R^2 and R^3 represent each H, F, cyano, acyl, nitro, alkyl, morpholino or R^1 ; R^4 and R^5 represent each H, hydroxy, alkyl, cycloalkyl, heterocycle, phenyl or Y-substituted alkyl; Y represents hydroxy, acyloxy, F-substituted methyl, cycloalkyl, tetrahydrofuryl, carboxyl, alkoxy carbonyl or NR^9R^{10} ; and R^9 and R^{10} represent H or alkyl, or alternatively R^9 and R^{10} are combined together to represent a 5- or 6-membered cyclic group which may contain oxygen atom(s).
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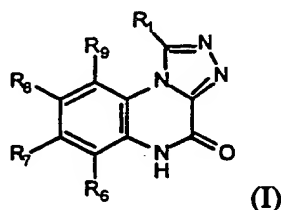
- 20 (3) Triazoloquinoxalin-1,4-diones (I) and (II) in WO 93-06103 an shown below:



Quinoxaline compounds represented by formula (I) or (II), wherein R^1 and R^2 are independently hydrogen, C_{1-6} -alkyl, halogen, NO_2 , NH_2 , CN , CF_3 , $SO_2NR^4R^5$ wherein

R^4 and R^5 are independently hydrogen or C_{1-6} -alkyl, or COR^6 wherein R^6 is C_{1-6} -alkyl; and R^3 is hydrogen, C_{1-6} -alkyl or CF_3 , and compositions thereof.

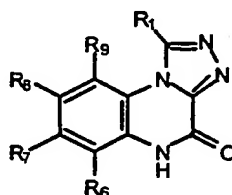
- 5 (4) [1,2,4]Triazolo[4,3-a]quinoxalinone derivatives (I) in WO 96-08493 A1 as shown below:



- 10 [1,2,4]triazolo[4,3-a]quinoxalinone compounds of general formula (I) wherein R^1 is $POX'X''$ or alkyl substituted with COX' or $POX'X''$, and X' and X'' independently are hydroxy or alkoxy, and R^6 , R^7 , R^8 and R^9 independently are hydrogen; alkyl; halogen; NH_2 ; NO_2 ; CN ; CF_3 $SO_2NY'Y''$ OR COZ' wherein Z' is $NY'Y''$ or alkyl and Y' and Y'' independently are hydrogen or alkyl; triazolyl; imidazolyl substituted with phenyl or alkyl.

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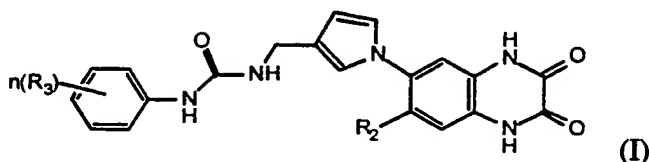
- (5) [1,2,4]Triazolo[4,3-a]quinoxalinone derivatives (I) in WO 96-08492 A1 as shown below:



- 20 [1,2,4]triazolo[4,3-a]quinoxalinone compounds of general formula (I) wherein R^1 is $POX'X''$ or alkyl substituted with COX' or $POX'X''$ and X' and X'' independently are hydroxy or alkoxy, and R^6 , R^7 , R^8 and R^9 independently are hydrogen; alkyl; halogen; NH_2 , NO_2 , CN , CF_3 , $SO_2NY'-Y''$, COZ' wherein Z' is $NY'Y''$ or alkyl and Y' and Y'' independently are hydrogen or alkyl; triazolyl; imidazolyl, piperidino, piperazinyl,

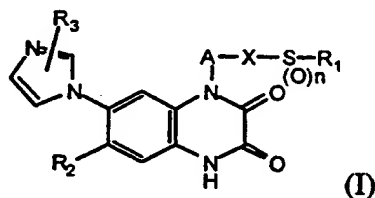
morpholino or thiomorpholino; all rings optionally being substituted.

(6) Pyrrolylquinoxalindiones (I) in WO 97 49701 as shown below:



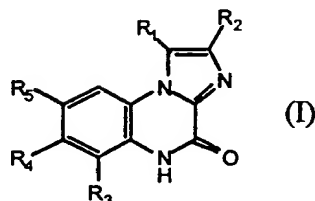
Pyrrolylquinoxalindiones of formula (I) and their tautomeric and isomeric forms and their physiologically acceptable salts, in which R^1 is hydrogen, C_1 - C_6 alkyl, substituted by hydroxyl or carboxyl, R_2 is hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, a chlorine, fluorine or bromine atom, a trihalogen methyl, cyano, or nitro group or $SO_2C_1C_4$ alkyl, R^3 is $COOH$ or a radical hydrolysable to form the carboxyl group, and n is 1 or 2.

(7) Imidazole-substituted quinoxalinedione derivatives (I) in WO 97-46555 as shown below:



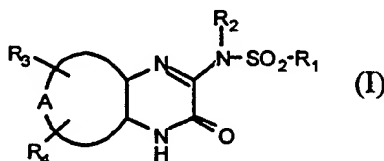
Substituted imidazole quinoxalinedione derivatives represented by general formula (I), wherein each symbol has the following meaning: A: $(CH_2)_m$ or $Ph-(CH_2)_p$ (Ph being phenyl); X: oxygen or NR^4 ; R^1 : hydrogen, hydroxy or triazolyl, provided that X may be a bond when R^1 is triazolyl; R^2 : hydrogen, nitro, halogenated lower alkyl, cyano, amino, mono - or di (lower alkyl)amino, or halogeno; R^3 and R^4 : the same or different and each representing hydrogen or lower alkyl; n : 0, 1 or 2; m : an integer of 2 to 6; and p : an integer of 1 to 6.

(8) Heterocyclically substituted imidazoloquinoxalines (I) in WO 97-34896 as shown below:



Imidazoloquinoxalines of formula (I), wherein R^1 to R^4 have the meanings given in the description in the corresponding patent (WO 97-34896) and R^5 is a five-member optionally substituted heterocycle with between 1 and 4 nitrogen atoms or with 1 or 2 nitrogen atoms and an oxygen or sulphur atom, or an R^6 -substituted phenyl ring.

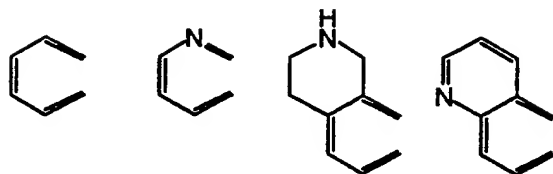
(9) Quinoxaline derivatives (I) in WO 97-32858 as shown below:



Quinoxaline derivatives of the formula (I) wherein R^1 is alkyl, halo (lower) alkyl, amino, aryl or heterocyclic group, R^2 is hydrogen or lower alkyl, R^3 and R^4 are each independently hydrogen, cyano, nitro, halogen, lower alkyl, halo (lower) alkyl, lower alkoxy, halo (lower) alkoxy, di (lower) -alkylamino, aryl which may have one or more substituents (s), heterocyclic group which may have one or more substituents (s), lower alkylthio which may have one or more substituents (s), heterocyclicthio, lower alkylsulfonyl, lower alkylaminosulfonyl, or heterocyclicsulfonyl, a group of the formula:

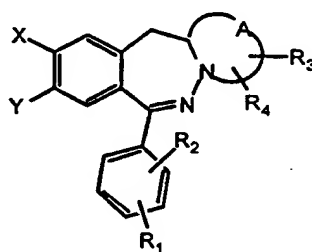


A is the group of the formula:



- 5 It is to be noted the object compound (I) may include one or more stereoisomers due to asymmetric carbon atom (s) and double bond, and all of such isomers and a mixture thereof are included. It is further to be noted that isomerization or rearrangement of the object compound (I) may occur due to the effect of the light, acid, base or the like, and the compound obtained as the result of said isomerization or rearrangement is also
- 10 included within the scope of the present invention. It is also to be noted that the solvating form of the compound (I) (e.g. hydrate, etc.) and any form of the crystal of the compound (I) are included within the scope of the present invention.

- 15 (10) Condensed 2,3-benzodiazepine derivatives (I) in WO 97-28163 as shown below:

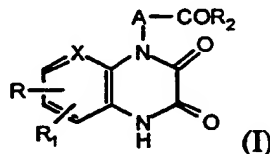


(I)

- 2,3-Benzodiazepine derivatives of the formula (I) wherein R^1 and R^2 are identical or different and hydrogen, C_1 - C_6 -alkyl, nitro, halogen, cyano, the group $-NR^8R^9$, $-O-C_1$ -4-alkyl, $-CF_3$, OH or C_1 -6-alkanoyloxy; R^3 and R^4 are identical or different and
- 20 hydrogen, halogen, C_1 - C_6 -alkoxy, hydroxy, thiocyanate, C_1 - C_6 -alkylthio, cyano, $COOR^{12}$, $PO_3R^{13}R^{14}$, C_1 - C_6 -alkanoyl, C_1 - C_6 -alkanoyloxy, eventually with C_1 - C_4 -

alkoxy or phenyl-substituted C₂₋₆-alkynyl, eventually with C₁₋₄-alkoxy or phenyl-substituted C₂₋₆-alkenyl, eventually with halogen, hydroxy, C₁₋₆-alkoxy, C₁₋₆-thioalkyl, NR¹⁰-R¹¹-substituted C₁₋₆-alkyl, C₃₋₇-cycloalkyl or eventually a substituted aryl- or hetaryl-rest; R⁸ and R⁹ are identical or different and hydrogen, C₁₋₆-alkyl or the group-CO-C₁₋₆-alkyl; R¹⁰ and R¹¹ are identical or different and hydrogen, C₁₋₆-alkyl or C₁₋₆-alkanoyl or together with the nitrogen atom will build a 5-7 branched saturated heterocyclus, which will contain and can be substituted with a further oxygen-, sulfur or nitrogen atom; R¹², R¹³, R¹⁴ are identical or different and H or C₁₋₆-alkyl; X hydrogen or halogen; Y C₁₋₆-alkoxy or X and Y together - O-(CH₂)_n-O-; n means 1,2 or 3 and A together with the nitrogen will form a saturated or an unsaturated 5 membered heterocyclus, which can contain 1-3 nitrogen atoms and/or a oxygen atom and/or one or two carbonyl groups or their isomers or physiological salts thereof.

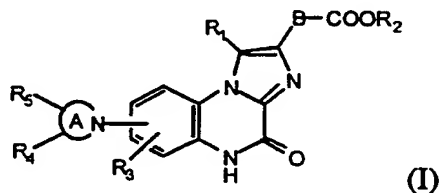
(11) 1,2,3,4-Tetrahydroquinoxalindione derivatives (I) in WO 96-10023 as shown below:



A 1,2,3,4-tetrahydroquinoxalindione derivative represented by general formula (I) or a salt thereof, an NMDA-glycine receptor and/or AMPA receptor antagonist and a kainate neurocytotoxicity inhibitor each containing the same, and a medicinal composition comprising the above-mentioned compound and pharmaceutically acceptable carriers: wherein X represents N or CH; R represents imidazolyl or di(lower alkyl)amino; R¹ represents (I) halogeno, nitro, cyano, carboxy, amino, mono- or di(lower alkyl) amino, lower alkanoyl, lower alkylthio, lower alkylsulfinyl, lower

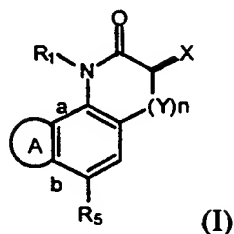
alkylsulfonyl, or carbamoyl, (2) lower alkyl or lower alkoxy which may be substituted by halogeno, carboxy or aryl, or (3) phenyloxy which may be substituted by lower alkoxycarbonyl or carboxy; R^2 represents hydroxy, lower alkoxy, amino, or mono- or di(lower alkyl)amino; and A represents optionally substituted alkylene or -O-B- (B being lower alkylene); provided the case wherein R represents imidazolyl, R^1 represents cyano, A represents ethylene and R^2 represents hydroxy is excepted.

(12) New heterocyclic substituted imidazoloquinoxalinones (I) in WO 96-10572 as shown below:



Imidazoloquinoxalinones of the formula (I), in which R^1 stands for hydrogen, branched or linear C_{1-5} -alkyl or a phenyl, pyridyl or thienyl group possibly substituted by one to two chlorine atoms, a trifluoromethyl, a nitrodioxy or a methylene dioxy group; R^2 stands for hydrogen, C_{1-5} -alkyl or C_{3-8} -dialkylaminoalkyl; R^3 stands for a chlorine or bromine atom, a trifluoromethyl, cyano or nitro group; A stands for a five-membered heterocycle with 1-4 nitrogen atoms or 1-2 nitrogen atoms and one oxygen or sulphur atom possible substituted by R^4 and R^5 ; the radicals R^4 and R^5 , that may be the same or different, stand for hydrogen, C_{1-5} -alkyl, C_{1-5} -hydroxyethyl, phenyl, phenyl substituted by a chlorine atom, a trifluoromethyl or nitro group, -CHO, -COOH, -COO- C_{1-5} -alkyl, -CH₂-NR⁶R⁷ (in which R^6 =H, C_{1-5} -alkyl, R^7 =H, C_{1-5} -alkyl), -CH₂-NH-CO-R⁸ (in which R^8 = C_{1-5} -alkyl, phenyl, a phenyl group or an heteroaryl group possibly substituted by a chlorine atom of a nitro or trifluoromethyl group) or -CH₂-NHCONHR⁸, and B stands for a bond or a C_{1-5} -alkylene chain. Also disclosed are the tautomer and isomer forms of these compounds, as well as their physiologically compatible salts.

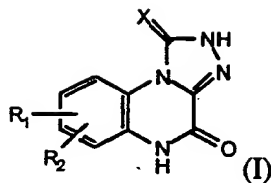
(13) Fused indole and quinoxaline derivatives (I) in WO 9608495 A1 as shown below:



Compounds having formula (I) or a pharmaceutically acceptable salt thereof wherein:
 R^1 is hydrogen, alkyl or benzyl; X is O or NOR^2 , wherein R^2 is hydrogen, alkyl or benzyl; Y is N-R^4 wherein R^4 is hydrogen, OH or alkyl; n is 0 or 1; R^6 is phenyl which is substituted one or more times with substituents selected from the group consisting of $\text{SO}_2\text{NR}'\text{R}''$, $\text{CONR}'\text{R}''$, and COR''' wherein R' and R'' each independently are hydrogen, alkyl, or $-(\text{CH}_2)_p\text{-W}$, wherein p is 0, 1, 2, 3, 4, 5, or 6, and W is hydroxy, amino, alkoxycarbonyl, or phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3 , NO_2 , amino, alkyl, alkoxy or methylenedioxy; or wherein R' and R'' together are $(\text{CH}_2)_r\text{Z}(\text{CH}_2)_s$, wherein r and s each independently are 0, 1, 2, 3, 4, 5 or 6 and Z is O, S, CH_2 or NR''' wherein R''' is hydrogen, alkyl, or $-(\text{CH}_2)_p\text{-W}$, wherein p is 0, 1, 2, 3, 4, 5 or 6, and W is hydroxy, amino, alkoxycarbonyl, or phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3 , NO_2 , amino, alkyl, alkoxy or methylenedioxy; and wherein R''' is hydrogen, alkyl, alkoxy or phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3 , NO_2 , amino, alkyl, alkoxy or methylenedioxy; A is a ring of five to seven atoms fused with the benzo ring at the positions marked a and b.

(14) [1,2,4]Triazolo[4,3-a]quinoxaline compounds (I) in WO 94-26746 as shown in below:

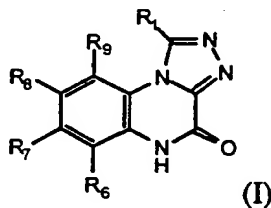
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5 [1,2,4]Triazolo[4,3-a]quinoxaline derivatives of general formula (I) wherein one of R^1 and R^2 is a 5- or 6-membered N- containing heterocyclic ring optionally substituted, or a fused ring system comprising a 5- or 6-membered N-containing heterocyclic ring optionally substituted; and the other of R^1 and R^2 is H, alkyl, alkoxy, halogen, NO_2 , NH_2 , CN, CF_3 , COC_{1-6} -alkyl or $SO_2NR'R''$, wherein R' and R'' are independently H or alkyl and X is O or S; and pharmaceutically acceptable salts thereof.

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(15) [1,2,4]Triazolo[4,3-a]quinoxaline derivatives (I) in WO 94-21639 as shown below:

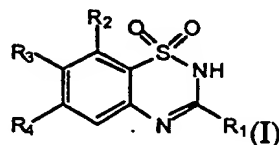


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Quinoxaline compounds of general formula (I) wherein R^1 is COX' , $POX'X''$ or alkyl substituted with COX'' OR $POX'X''$, and X' and X'' independently are hydroxy or alkoxy, and R^6 , R^7 , R^8 and R^9 independently are hydrogen, alkyl, halogen, NH_2 , NO_2 , CN, CF_3 , $SO_2NY'Y''$ or COZ' wherein Z' is $NY'Y''$ or alkyl and Y' and Y'' independently are hydrogen or alkyl, triazolyl, imidazolyl, imidazolyl substituted with phenyl or alkyl, or R^6 and R^7 , or R^8 and R^9 , together form a further fused ring.

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(16) 2H-1,2,4-Benzothiadiazine-1,1-dioxide-3-carboxylic acid derivatives (I) WO 93-21171 as shown below:



5 The present invention relates to the use of derivatives of the 2H-1,2,4-benzothiadiazine-1,1-dioxide-3-carboxylic acid of the above formula or the salts of such compound or of intermediates of such compound for the preparation of AMPA receptor antagonists and to new compounds of the formula (I), their preparation and the medications in which they are found.

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In the formula (I): R₁ is carboxy, alkoxycarbonyl, tetrazolyl, -CO-NH₂, -CO-NH-alk, -CO-N(alk)₂, -CO-NHOH, -CO-N(alk)OH, -CO-NH-O-R₅, -CO-N(alk)-OR₅ or a group that may be converted into a carboxyl moiety in vivo; R₂, R₃ and R₄ are the same or different and are selected from the group consisting of hydrogen, halogen or alkyl; R₅ is alkyl or phenylalkyl.

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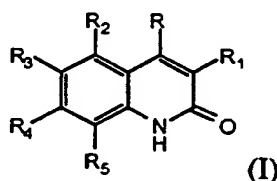
The term alk refers to an alkyl or alkylene group. Clearly, the compounds of the present invention include the tautomers of the compounds of the formula (I). The groups, convertible into carboxyl moieties in vivo, include -CO-R₆, in which R₆ is O-alk-R₇, -O-alk-O-CO-alk, -O-alk-O-COOalk, -O-alk-O-CO-R₇, -O-alk-OH, -O-alk-O-alk, -O-alk-S-alk, -O-alk-O-R₇, -O-alk-S-R₇, -O-alk-COOH, -O-alk-COOalk, -O-alk-NR₈R₉, -NH-alk-O-CO-alk, -NH-alk-O-COOalk, -NH-alk-O-CO-R₇, -NH-alk-OH, -NH-alk-O-alk, -NH-alk-S-alk, -NH-alk-O-R₇, -NH-alk-S-R₇, -NH-alk-COOH, -NH-alk-COOalk, -NH-alk-NR₈R₉. In these definitions, R is alkyl or alkylene, R₇ phenyl, R₈ and R₉ are the same or different and are selected from the group consisting of hydrogen, alkyl, phenyl or phenylalkyl or form with the oxygen atom they are attached to a piperidiny, morpholinyl or pyrrolidinyl ring. The halogen atoms are selected from the following: fluoride, chloride, bromide or iodide. Unless otherwise

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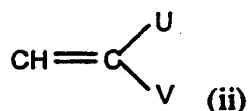
stated, in the above and below definitions, the alkyl, alkoxy and alkylene groups are a straight or branched alkyl chain having one to six carbon atom, and preferably one to four carbon atoms. The compounds of the formula (I) in which either R₂, R₃ and R₄ are hydrogen and R₁ is carboxy, alkoxycarbonyl, -CO-NH₂ or -CO-NH-alk, or R₄ a chloride or bromide atom, R₂ and R₃ are hydrogen and R₁ is carboxy, alkoxycarbonyl, -CO-NH₂ or -CO-NH-alk, or R₃ a chloride or bromide atom, R₂ and R₄ are hydrogen and R₁ is carboxy, alkoxycarbonyl, -CO-NH₂ or -CO-NH-alk. The present invention include also other compounds of the formula (I), their salts or intermediates of their salts. In these compounds, R₁ is carboxy, alkoxycarbonyl, tetrazolyl, -CO-NH₂, -CO-NH-alk, -CO-N(alk)₂, -CO-NHOH, -CO-N(alk)OH, CO-NH-O-R₅, CO-N(alk)-OR₅ or -CO-R₆, in which R₆ is -O-alk-R₇, -O-alk-O-CO-alk, -O-alk-O-COOalk, -O-alk-O-CO-R₇, -O-alk-OH, -O-alk-O-alk, -O-alk-S-alk, -O-alk-O-R₇, -O-alk-S-R₇, -O-alk-COOH, -O-alk-COOalk, -O-alk-NR₈R₉, -NH-alk-O-CO-alk, -NH-alk-O-COOalk, -NH-alk-O-CO-R₇, -NH-alk-OH, -NH-alk-O-alk, -NH-alk-S-alk, -NH-alk-O-R₇, -NH-alk-S-R₇, -NH-alk-COOH, -NH-alk-COOalk, -NH-alk-NR₈R₉, R₂, R₃ and R₄ are the same or different and are selected from the group consisting of hydrogen, halogen or alkyl, R₅ is alkyl or phenylalkyl, R₇ is phenylalkyl, R₈ and R₉ are the same or different and are selected from the group consisting of hydrogen, alkyl, phenyl or phenylalkyl or form with the oxygen atom they are attached to a piperidinyl, morpholinyl or pyrrolidinyl ring. The term alk refers to an alkyl or alkylene group. The present invention does not include the compounds of the formula (I) in which either R₂, R₃ and R₄ are hydrogen and R₁ is carboxy, alkoxycarbonyl, -CO-NH₂ or -CO-NH-alk, or R₄ a chloride or bromide atom, R₂ and R₃ are hydrogen and R₁ is carboxy, alkoxycarbonyl, -CO-NH₂ or -CO-NH-alk, or R₃ a chloride or bromide atom, R₂ and R₄ are hydrogen and R₁ is carboxy, alkoxycarbonyl, -CO-NH₂ or -CO-NH-alk.

hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, -OR^a, -SR^a, -SOR^a, -SO₂R^a, -SO₂NR^aR^b, -NR^aR^b, NR^aCOR^b, -NR^aCO₂R^b, -COR^a, -CO₂R^a or -CONR^aR^b; or R¹ and R² together represent the residue of a carbocyclic or heterocyclic ring; one of R³, R⁴, R⁵ and R⁶ represents hydrogen, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, -OR^a, -SR^a, -SOR^a, -SO₂R^a, -SO₂NR^aR^b, -NR^aR^b, -NR^aCOR^b, -NR^aCO₂R^b, -COR^a, -CO₂R^a or -CONR^a or -CONR^aR^b, and the other three of R³, R⁴, R⁵ and R⁶ independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, -OR^a, -SR^a, -SOR^a, -SO₂R^a, -SO₂NR^aR^b, -NR^aR^b, -NR^aCOR^b, -NR^aCO₂R^b, -COR^a, -CO₂R^a or -CONR^aR^b, and R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group.

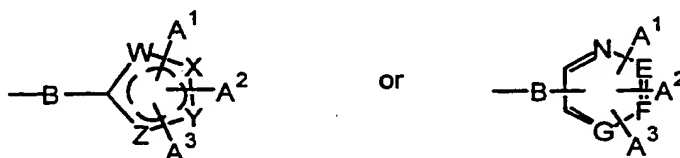
(19) Quinolone derivatives (I) in WO 93-10783 as shown below:



Compounds of formula I or a pharmaceutically acceptable salt thereof or a prodrug thereof wherein R represents a hydrogen atom, an amino group, a carboxy or C₂₋₆ alkoxy carbonyl group, or a group of formula -α-β-ε, in which α represents a chemical bond, an oxygen or sulphur atom, or an -NH- group; β represents a carbonyl (C=O) or sulphonyl (SO₂) group, or a straight or branched alkylene chain containing from 1 to 6 carbon atoms; and ε represents C₁₋₆ alkyl, C₂₋₆ alkenyl, phenyl, -NR^aR^b, -CO₂R^a or -CH₂CO₂R^a; R¹ is a group of part formula (i) or (ii):

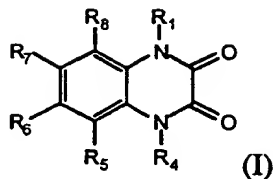


- wherein U and V independently represent cyano, carboxy, $-\text{COR}^6$, $-\text{CO}_2\text{R}^6$, $-\text{CO.SR}^6$, $-\text{CONHOH}$ or $-\text{CONHNH}_2$; n is zero or 1, preferably zero; T represents cyano, carboxy, $-\text{COR}^6$, $-\text{CO}_2\text{R}^6$, $-\text{CO.SR}^6$, $-\text{CONHOH}$, $-\text{CONHNH}_2$ or a group of formula
- 5 in which the broken circle represents two non-adjacent double bonds in any position in the five-membered ring; B represents a bond or a carbonyl group ($\text{C}=\text{O}$); W, X, Y and Z independently represent oxygen, sulphur, nitrogen or carbon, provided that no more than one of W, X, Y and Z represents oxygen or sulphur and at least one of W, X, Y and Z is other than carbon; one of E, F and G represents nitrogen or carbon and the remainder represent carbon; A^1 , A^2 and A^3 represent one, two or three substituents not
- 10 exceeding the maximum number permissible by the disposition of heteroatoms in the five- or six-membered ring, which substituents are independently selected from hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-\text{OR}^a$, $-\text{SR}^a$, $-\text{SOR}^a$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{COR}^b$, $-\text{NR}^a\text{CO}_2\text{R}^b$, $-\text{COR}^a$, $-\text{CO}_2\text{R}^a$ or $-\text{CONR}^a\text{R}^b$; or A^1 and A^2 or A^2 and A^3 together represent the residue of an
- 15 aromatic or heteroaromatic ring;



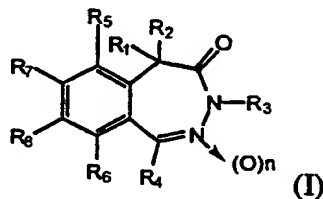
- one of R^2 , R^3 , R^4 and R^5 represents hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-\text{OR}^a$, $-\text{SR}^a$, $-\text{SOR}^a$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{COR}^b$, $-\text{NR}^a\text{CO}_2\text{R}^b$, $-\text{COR}^a$, $-\text{CO}_2\text{R}^a$ or $-\text{CONR}^a\text{R}^b$, and the other three of R^2 , R^3 , R^4 and R^5 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-\text{OR}^a$, $-\text{SR}^a$, $-\text{SOR}^a$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{COR}^b$, $-\text{NR}^a\text{CO}_2\text{R}^b$, $-\text{COR}^a$, $-\text{CO}_2\text{R}^a$ or $-\text{CONR}^a\text{R}^b$; or R^2 and R^3 , R^3 and R^4 or R^4 and R^5
- 20 together represent the residue of an aromatic or heteroaromatic ring; R^6 represents hydrocarbon or a heterocyclic group; and R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group.
- 25

(20) Quinoxaline derivatives (I) in WO 93-08173 as shown below:



- 5 Quinoxaline derivatives of the formula (I), in which R^1 is C_{1-12} -alkyl substituted by R^2 , C_{2-12} -alkenyl substituted by R^2 , C_{2-12} -alkynyl substituted by R^2 , C_{3-7} -cycloalkyl substituted by R^2 , $-(CH_2)_n$ - C_{6-12} -aryl substituted by R^2 in the aryl or alkyl residue or $-(CH_2)_n$ -hetaryl substituted by R^2 in the hetaryl or alkyl residue; R^4 is hydrogen, C_{1-12} -alkyl substituted by R^2 , C_{2-12} -alkenyl substituted by R^2 , C_{2-12} -alkynyl substituted by R^2 , $(CH_2)_n$ - C_{6-12} -aryl substituted by R^2 in the aryl or alkyl residue, or $-(CH_2)_n$ -hetaryl substituted by R^2 in the hetaryl or alkyl residue; R^5 , R^6 , R^7 and R^8 are the same or different and represent hydrogen, halogen, nitro, NR^9R^{10} , $NHCO R^{11}$, SO_2R^{12} , C_{3-7} -cycloalkyloxy, COR^{13} , cyano, CF_3 , C_{1-6} -alkyl, C_{1-4} -alkoxy or imidazole possibly substituted by cyano, C_{1-4} -alkyl or $-COO-C_{1-6}$ -alkyl or R^5 and R^6 or R^7 and R^8 represent a condensed benzene ring, and R^2 stands for $-CO-R^3$, or $-PO-XY$ and is present once or twice in the same or a different form.

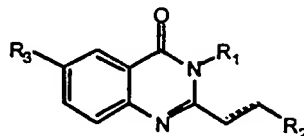
(21) Substituted 2,3-benzodiazepin-4-one (I) in WO 97-34878 as shown below:



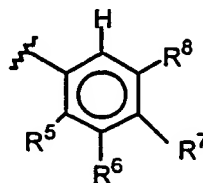
Substituted 2,3-benzodiazepin-4-one represented by formula (I) or a pharmaceutically acceptable salt or prodrug thereof, wherein: R_1 and R_2 are independently hydrogen, alkyl, haloalkyl, aryl, fused aryl, a carbocyclic group, a heterocyclic group, a

heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl or thioalkyl; or R_1 and R_2 are taken together to form a carbocycle or heterocycle; R_3 is hydrogen, alkyl, haloalkyl, aryl, fused aryl, a carbocyclic group, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, COR, CO_2R and $CONR_xR_y$, wherein R , R_x and R_y are independently hydrogen, alkyl, haloalkyl, aryl, fused aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, or aminoalkyl; or R_x and R_y are taken together to form a carbocycle or heterocycle; R_4 is substituted or unsubstituted aryl, fused aryl, a carbocyclic group, a heterocyclic group, or a heteroaryl group; R_5 and R_6 are independently hydrogen, halo, haloalkyl, aryl, fused aryl, a carbocyclic group, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, carboxy, carbonylamido or alkylthiol; R_7 and R_8 are independently hydrogen, halo, haloalkyl, aryl, fused aryl, a carbocyclic group, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido or alkylthiol; or R_7 and R_8 are taken together to form a carbocycle or heterocycle, for example, $-OCH_2O-$, $-(CH_2)_3-$, $-(CH_2)_4$, $-OCH_2CH_2O-$, $-CH_2N(R)CH_2-$, $-CH_2CH_2N(R)CH_2-$, $-CH_2N(R)CH_2CH_2-$, $-N(Me)-C(O)-O-$ and $-N=C-C=N-$, wherein R is as defined above; and n is 0 or 1.

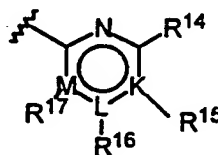
(22) 2,3-Disubstituted-4(3H)-quinazolinone in WO97-43276 as shown below:



Bicyclic compounds of the formula wherein R^1 is optionally substituted phenyl of the formula Ph^1 or heteroaryl wherein said heteroaryl is selected from the group consisting of pyridin-2-yl, pyridin-3-yl and pyridin-4-yl, wherein said heteroaryl may optionally be substituted on any of the ring carbon atoms capable of forming an additional bond, up to a maximum of three substituents per ring, with a substituent selected from hydrogen, (C₁-C₆)alkyl, halogen, trifluoromethyl, amino-(CH₂)_n-, (C₁-C₆)alkylamino-(CH₂)_n-, di(C₁-C₆)alkyl-amino-(CH₂)_n-, (C₁-C₆)alkoxy, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkyl-O-(C₁-C₆)alkyl-, -CN, (C₁-C₆)alkyl-C-O-, (C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-C-O-(C₁-C₆)alkyl, (C₁-C₆)alkyl-C-O-, hydroxy, H-C(=O)-, (C₁-C₆)alkyl-C(=O)-(CH₂)_n-, HO-C(=O)-(CH₂)_n-, (C₁-C₆)alkyl-O-C(=O)-(CH₂)_n-, NH₂-C(=O)-(CH₂)_n-, (C₁-C₆)alkyl-NH-C(=O)-(CH₂)_n-, and di(C₁-C₆)alkyl-NH-C(=O)-(CH₂)_n, wherein said Ph^1 is a group of the formula

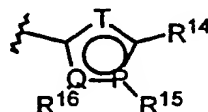


R^2 is phenyl of the formula Ph^2 or a five or six membered heterocycle, wherein said 6-membered heterocycle has the formula

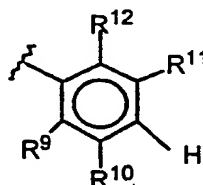


wherein "N" is nitrogen; wherein said ring positions "K", "L" and "M" may be

independently selected from carbon or nitrogen, with the proviso that i) only one of "K", "L" or "M" can be nitrogen and ii) when "K", "L" or "M" is nitrogen then its respective R^{15} , R^{16} or R^{17} is absent; wherein said five membered heterocycle has the formula



wherein said "T" is -CH-, N, NH, O or S; wherein said ring positions "P" and "Q" may be independently selected from carbon, nitrogen, oxygen or sulfur; with the proviso that only one of "P", "Q" or "T" can be oxygen or sulfur and at least one of "P", "Q" or "T" must be a heteroatom; wherein said Ph^2 is a group of the formula

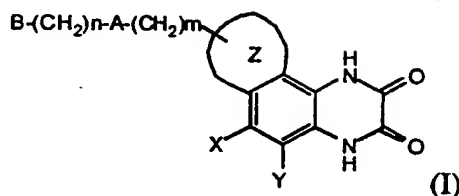


R^3 is hydrogen, halo, -CN, -NO₂, CF₃, (C₁-C₆)alkyl or (C₁-C₆)alkoxy; R^5 is hydrogen, (C₁-C₆)alkyl, halo, CF₃, (C₁-C₆)alkoxy or (C₁-C₆)alkylthiol; R^6 is hydrogen or halo; R^7 is hydrogen or halo; R^8 is hydrogen or halo; R^9 is hydrogen, halo, CF₃, (C₁-C₆)alkyl optionally substituted with one to three halogen atoms, (C₁-C₆)alkoxy optionally substituted with one to three halogen atoms, (C₁-C₆)alkylthiol, amino-(CH₂)_s-, (C₁-C₆)alkyl-NH-(CH₂)_s-, di(C₁-C₆)alkyl-N-(CH₂)_s-, (C₃-C₇)cycloalkyl-NH-(CH₂)_s-, H₂N-(C=O)-(CH₂)_s-, (C₁-C₆)alkyl-HN-(C=O)-(CH₂)_s-, di(C₁-C₆)alkyl-N-(C=O)-(CH₂)_s-, (C₃-C₇)cycloalkyl-NH-(CH₂)_s-, $R^{13}O$ -(CH₂)_s-, $R^{13}O$ -(C=O)-(CH₂)_s-, H(O=C)-NH-(CH₂)_s-, (C₁-C₆)alkyl-(O=C)-n-(CH₂)_s-, H(O=C)-(CH₂)_s-, (C₁-C₆)alkyl-(C=O)-, hydroxy, hydroxy-(C₁-C₆)alkyl, (C₁-C₆)alkyl, (C₁-C₆)alkyl-, (C₁-C₆)alkyl-O-(C₁-C₆)alkyl-, and -CN; R^{10} and R^{14} are selected, independently, from hydrogen, halo,

CF₃, (C₁-C₆)alkyl optionally substituted with one to three halogen atoms, (C₁-C₆)alkoxy optionally substituted with one to three halogen atoms, (C₁-C₆)alkylthiol, amino-(CH₂)_p-, (C₁-C₆)alkyl-NH-(CH₂)_p-, di(C₁-C₆)alkyl-N-(CH₂)_p-, amino-(C₁-C₆)alkyl-NH-(CH₂)_p-, (C₁-C₆)alkyl-NH-(C₁-C₆)alkyl-NH-(CH₂)_p-, di(C₁-C₆)alkyl-N-(C₁-C₆)alkyl-NH-(CH₂)_p-, di(C₁-C₆)alkyl-N-(C₁-C₆)alkyl-N-(CH₂)_p-, H₂N-(C=O)-(CH₂)_p-, H₂N-(C=O)-(CH₂)_p-, (C₁-C₆)alkyl-HN-(C=O)-(CH₂)_p-, (C₃-C₇)cycloalkyl-NY-(C=O)-(CH₂)_p-, R¹³O-(C=O)-(CH₂)_p-, H(O=C)-O-, H(O=C)-O-(C₁-C₆)alkyl-, H(O=C)-NH-(CH₂)_p-, (C₁-C₆)alkyl-(O=C)-NH-(CH₂)_p-, -CHO, H-C(C=O)-(CH₂)_p-, (C₁-C₆)alkyl-(C=O)-(CH₂)_p-, (C₁-C₆)alkyl-(O=C)-N-(CH₂)_p-, H(O=C)-N-(CH₂)_p-, HO-(C₁-C₆)alkyl-N-(CH₂)_p-, (C₁-C₆)alkyl-(C=O)-O-NH-(CH₂)_p-, amino-(C₁-C₆)alkyl-(C=O)-O(CH₂)_p-, (C₁-C₆)alkyl-, (C₁-C₆)alkyl-NH-(C₁-C₆)alkyl-(C=O)-O-(CH₂)_p-, di(C₁-C₆)alkyl-N-(C₁-C₆)alkyl-(C=O)-O-(CH₂)_p-, amino-(C₁-C₆)alkyl-O-(C=O)-(CH₂)_p-, (C₁-C₆)alkyl-NH-(C₁-C₆)alkyl-O-(C=O)-(CH₂)_p-, di(C₁-C₆)alkyl-N-(C₁-C₆)alkyl-O-(C=O)-(CH₂)_p-, hydroxy, hydroxy-(C₁-C₆)alkyl-, hydroxy-(C₁-C₆)alkyl-NH-(CH₂)_p-, (C₁-C₆)alkyl-O-(C₁-C₆)alkyl-, -CN, piperidine-(CH₂)_p-, pyrrolidine-(CH₂)_p-, and 3-pyrroline-(CH₂)_p-, wherein said piperidine, pyrrolidine and 3-pyrroline of said piperidine-(CH₂)_p-, pyrrolidine-(CH₂)_p- and 3-pyrroline-(CH₂)_p- moieties may optionally be substituted on any of the ring carbon atoms capable of supporting and additional bond, preferably zero to two substituents, with a substituent independently selected from halo, CF₃, (C₁-C₆)alkyl optionally substituted with one to three halogen atoms, (C₁-C₆)alkoxy optionally substituted with one to three halogen atoms, (C₁-C₆)alkylthiol, amino-(CH₂)_p-, (C₁-C₆)alkyl-NH-(CH₂)_p-, di(C₁-C₆)alkyl-N-(CH₂)_p-, (C₃-C₇)cycloalkyl-NH-(CH₂)_p-, amino-(C₁-C₆)alkyl-NH-(CH₂)_p-, (C₁-C₆)alkyl-NH-(C₁-C₆)alkyl-NH-(CH₂)_p-, di(C₁-C₆)alkyl-N-(C₁-C₆)alkyl-NH-(CH₂)_p-, (C₁-C₆)alkyl-O-(C₁-C₆)alkyl-, di(C₁-C₆)alkyl-N-(C₁-C₆)alkyl-N-(CH₂)_p-, H₂N-(C=O)-(CH₂)_p-, (C₁-C₆)alkyl-HN-(C=O)-(CH₂)_p-, di(C₁-C₆)alkyl-N-(C=O)-(CH₂)_p-, C₃-C₇cycloalkyl-NH-(C=O)-(CH₂)_p-, R¹³O-(CH₂)_p-, R¹³O-(C=O)-(CH₂)_p-, H(O=C)-O-, H(O=C)-O-(C₁-C₆)alkyl-, H(O=C)-NH-(CH₂)_p-, (C₁-C₆)alkyl-(O=C)-NH-(CH₂)_p-, -CHO, H-(C=O)-(CH₂)_p-, (C₁-C₆)alkyl-(C=O)-, (C₁-C₆)alkyl-(O=C)-N-(CH₂)_p-, H(O=C)-n-(CH₂)_p-, HO-(C₁-C₆)alkyl-N-(CH₂)_p-, (C₁-C₆)alkyl-(C=O)-O-NH-(CH₂)_p-, amino-(C₁-C₆)alkyl-

(C=O)-O-(CH₂)_p-, (C₁-C₆)alkyl-NH-(C₁-C₆)alkyl-(C=O)-O-(CH₂)_p-, di(C₁-C₆)alkyl-N-(C₁-C₆)alkyl-(C=O)-O-(CH₂)_p-, hydroxy, hydroxy-(C₁-C₆)alkyl-, hydroxy-(C₁-C₆)alkyl-NH-(CH₂)_p-, and -CN; R¹¹ is hydrogen or halo; R¹² is hydrogen, -CN or halo; R¹³ is hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkyl-(C=O)-, (C₁-C₆)alkyl-O-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)-, or di(C₁-C₆)alkyl-N-(C=O)-; R¹⁵ is hydrogen, -CN, (C₁-C₆)alkyl halo, CF₃, -CHO or (C₁-C₆)alkoxy; R¹⁶ is hydrogen, -CN, (C₁-C₆)alkyl, halo, CF₃, -CHO or (C₁-C₆)alkoxy; R¹⁷ is hydrogen, -CN, (C₁-C₆)alkyl, amino-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-NH-(C₁-C₆)alkyl-, di(C₁-C₆)alkyl-N-(C₁-C₆)alkyl-, halo, CF₃, -CHO or (C₁-C₆)alkoxy; n is an integer from zero to 3; each p is independently an integer from zero to 3; s is an integer from zero to 4; wherein the dashed bond represented an optional double bond; with the proviso that: i) when R⁹ is hydrogen, one of R¹¹ and R¹² is other than hydrogen; ii) when R¹ is unsubstituted phenyl and R³ is hydrogen then (a) R² can not be unsubstituted phenyl, thienyl or furyl or (b) R⁹ can not be Cl or hydroxy when R¹⁰ and R¹¹ are hydrogen, or (c) R¹⁰ or R¹¹ can not be chloro when R⁹ and R¹² are hydrogen; iii) when R³ is hydrogen; R⁶, R⁷ and R⁸ are hydrogen; and R⁵ is chloro or methyl, then (a) R² can not be unsubstituted phenyl, thienyl or furyl or (b) R¹⁰ or R¹¹ can not be chloro or (c) R⁹ or R¹² can not be hydroxy, methyl or methoxy; iv) when R³ is hydrogen or chloro; R⁵ is methyl; R⁶, R⁷ and R⁸ are hydrogen; and K, L and M equal carbon, then (a) one of R¹⁴ through R¹⁷ must be other than hydrogen or (b) R¹⁷ must be other than hydrogen or methyl; v) when R¹ is unsubstituted pyridin-2-yl and R³ is hydrogen, bromo or iodo then R² can not be unsubstituted phenyl; vi) when R⁷ is chloro; R⁵, R⁶, and R⁸ are hydrogen; and R³ is hydrogen, then (a) R² can not be unsubstituted phenyl, pyridyl, thienyl or furyl or (b) R⁹ or R¹² can not be hydroxy when R¹⁰ and R¹¹ are hydrogen; vii) when R² is unsubstituted phenyl, R⁶, R⁷ and R⁸ are hydrogen, and R³ is hydrogen, then R⁵ can not be -CO₂H; viii) when R² is unsubstituted pyridin-2-yl, R⁵ and R⁷ are hydrogen, then R⁶ or R⁸ must be other than chloro; ix) when R² is unsubstituted phenyl, R³ is hydrogen, and R⁵ and R⁷ are hydrogen, then one of R⁶ or R⁸ must be other than chloro; and the pharmaceutically acceptable salts of such compounds.

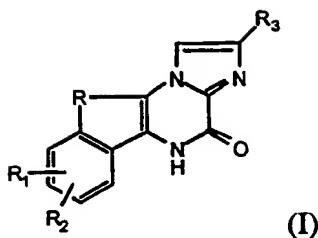
(23) Fused cycloalkyl quinoxalinedione (I) in WO 98-05651 as shown below:



- 5 Compounds represented by the formula (I) or pharmaceutically acceptable salts thereof wherein Z is a carbocyclic fused ring having 5 to 7 carbon atoms; X and Y are independently hydrogen, halogen, nitro, cyano, $-\text{CF}_3$, $-\text{COOH}$, $-\text{CONR}^1\text{R}^2$, $-\text{COR}^3$, $-\text{SO}_2\text{R}^3$, imidazolyl or imidazolidinyl, wherein R^1 and R^2 are independently hydrogen, alkyl having 1 to 6 carbon atoms, cycloalkyl, aralkyl or join together to form a heterocyclic ring and wherein R^3 is alkyl, haloalkyl, cycloalkyl, aryl or aralkyl; A is a bond, O, S, NR^4 , NR^4CO , NR^4CS , CONR^4 , CSNR^4 , CO or CS wherein R^4 is hydrogen, alkyl having 1 to 6 carbon atoms, cycloalkyl, aralkyl or when $n = 0$ then R^4 and B may join together to form a heterocyclic ring; B is hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, R^5 , CN, COR^5 , PO_3R^5_2 , SO_2R^5 , or heterocyclic, wherein R^5 is hydroxy, alkoxy, aralkoxy, aryloxy or NR^1R^2 ; and m and n are independently 0, 1, and 2, provided that (i) m is not 0 when A is 0, CN, tetrazole or CO, except when A is CO and B is a heterocyclic or when A is 0 and B is COR^5 , PO_3R^5_2 or SO_2R^5 ; (ii) m is not 0 or 1 when A is NR^4 , except when B is COR^5 , PO_3R^5_2 or SO_2R^5 ; and (iii) n is not) when A is 0, S, NR^4 , CONR^4 and B is NR^1R^2 , CN, COR^5 , or PO_3R^5_2 .

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(24) Imidazo[1,2-a]indeno[1,2-e]pyrazine-2-carboxylic acid derivatives (I) and their salts as shown in WO 96-02544 A1 as shown below:



Imidazo[1,2-a]indeno[1,2-e]pyrazine-2-carboxylic acid derivatives having general formula (I) wherein R is N-alk, C(R₄)R₅, CH-R₆ or C=R₇, R₁ and R₂ are the same or different and are selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, amino, -N=CH-N(alk)alk', nitro, cyano, phenyl, imidazolyl, SO₃H, hydroxy, polyfluoralkoxy, carboxy, alkylcarbonyl, -NH-CO-NR₁₁R₁₂, -N(alk)-CO-NR₁₁R₁₂, -N(alk-Ar)-CO-NR₁₁R₁₂, -NH-CS-NR₁₁R₁₂, -N(alk)-CS-NR₁₁R₁₂, -NH-CO-NR₁₁, -NH-CS-R₂₄, -NH-C(=NR₂₇)-NR₁₀R₁₂, -N(alk)-C(=NR₂₇)-NR₁₀R₁₂, -CO-NR₁₀R₁₂, -NH-SO₂-NR₁₀R₁₂, N(alk)-SO₂-NR₁₀R₁₂, -NH-SO₂-CF₃, -NH-SO₂-alk, -NR₁₀R₁₃, S(O)_m-alk-Ar, -SO₂-NR₁₀R₁₂, 2-oxo-1-imidazolidinyl in which position 3 may be substituted by an alkyl group, or 2-oxo-1-perhydropyrimidinyl in which position 3 may be substituted by an alkyl group, R₃ is carboxy, alkoxy carbonyl or carboxamide, R₄ is alkyl, -alk-Het or phenylalkyl in which the phenyl group is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₁₀, and -alk-COOR₁₀, R₅ is an alkyl group (the term C₁-C₁₁ alkyl represents a straight or branched alkyl chain having one to eleven carbon atoms), -alk-Het, NR₈R₉, -NH-CHO, -NH-COOR₁₇, -NH-SO₂R₂₄, -COOR₁₀, -alk-COOR₁₀, -alk-CONR₁₀R₁₈, -alk-NR₁₀R₁₈, -alk-OH, -alk-CN, phenylalkyl in which the phenyl group is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₁₀, and -alk-COOR₁₀, -NH-CO-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₁₀, and -alk-COOR₁₀, -NH-CO-Het, -NH-CO-alk-Het, -NH-CO-alk-COOR₁₀, -NH-CO-alk-NR₁₀R₁₈, -NH-CO-alk-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₁₀, and -alk-COOR₁₀, pyrrol-1-yl possibly substituted by -COOR₁₀, -NH-CO-

NH-alk-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₁₀, and -alk-COOR₁₀, -NH-CO-NH-Het, -NH-CO-NH-alk-Het, -NH-CO-NH-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₁₀, and -alk-COOR₁₀, -NH-COalk, -NH-COcycloalkyl, -NH-CO-NH-alk or -NH-CO-NH₂, or R₄ and R₅, together with the carbon atom they attached to, are a cycloalkyl group, R₆ is hydrogen, hydroxy, alkyl (the term C₁-C₁₁ alkyl represents a straight or branched alkyl chain having one to eleven carbon atoms), -alk-OH, -NR₁₄R₁₅, -alk-NR₁₄R₁₅, alk-Het, -NH-CHO, -COOalk, -alk-COOR₁₀, -alk-CO-NR₁₀R₂₁, phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₁₀, and -alk-COOR₁₀, -R₁₆-COOR₁₀, -CO-COOR₁₀ or pyrrol-1-yl which may be substituted by -COOR₁₀, or 2-oxo-2,5-dihydropyrrol-1-yl, R₇ is oxygen or NOH, NO-alk-COOR₁₀, NO-alk, CHR₁₉, NR₁₀, C(COOR₁₀)R₂₀ or C(CONR₁₀R₂₁)R₂₀, R₈ is hydrogen, alkyl, -alk-COOR₁₀, -alk-NR₁₀R₂₁, -alk-Het or phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₁₀ and -alk-COOR₁₀, R₉ is hydrogen or alkyl, R₁₀ is hydrogen or alkyl, R₁₁ is hydrogen, alkyl (the term C₁-C₉ alkyl represents a straight or branched alkyl chain having one to nine carbon atoms), -alk-COOR₁₀, alk-Het, -alk-NR₁₂R₁₀, phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, carboxy, alkoxycarbonyl, cyano, and -alk-COOR₁₀ or Het, phenyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, carboxy, alkoxycarbonyl, cyano, and -alk-COOR₁₀ or Het, R₁₂ is hydrogen or alkyl, R₁₃ is alkyl, Het or alkoxycarbonyl, R₁₄ and R₁₅ are the same or different and are each an alkyl group or R₁₄ is hydrogen and R₁₅ is hydrogen, alkyl, -COR₂₂, -CSR₂₃ or SO₂R₂₄, R₁₆ is a -CHOH or -CH(OH)-alk(C₁-C₅) chain, R₁₇ is alkyl or phenylalkyl, R₁₈ is hydrogen or alkyl, R₁₉ is hydroxy, alkyl, alk-Het, -NR₂₅R₂₆, -alk-COOR₁₀, -Het, phenyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl,

alkoxy, nitro, amino, hydroxy, -alk-NH₂, -COOR₁₀, cyano, and -alk-COOR₁₀, or, phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, carboxy, alkoxy, carbonyl, cyano, and -alk-COOR₁₀, R₂₀ is hydrogen or alkyl, R₂₁ is hydrogen or alkyl, R₂₂ is alkyl, cycloalkyl, -COOalk, -alk-COOR₁₀, phenyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, -COOR₁₀, cyano, and -alk-COOR₁₀, phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, -COOR₁₀, cyano and -alk-COOR₁₀, -alk-NR₁₀R₁₂, -NH-Ar in which Ar may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, -COOR₁₀, cyano, and -alk-COOR₁₀, -Het, -alk-Het, -OR₁₇, -NH-alk-Ar in which Ar may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, carboxy, alkoxy, carbonyl, -COOR₁₀, cyano and -alk-COOR₁₀, NH-alk-Het, -NH-alk, -NH₂ or -NH-Het, R₂₃ is -NH-alk, -NH-Ar, -NH-Het or -NH₂, R₂₄ is alkyl or phenyl, R₂₅ and R₂₆ are the same or different and are each alkyl or cycloalkyl, R₂₇ is hydrogen or alkyl.

The term alk refers to an alkyl or alkylene group. The term alk' refers to an alkyl group, m = 0, 1 or 2. The term Ar refers to a phenyl group. The term Het refers to a heterocycle which is mono or poly saturated or unsaturated with four to nine carbon atoms and one or more heteroatom (O, S, N) which may be substituted with one or more of the following: alkyl, phenyl, or phenylalkyl.

Unless otherwise stated, in the above and below definitions, the alkyl or alkylene groups are a straight or branched alkyl chain having one to six carbon atom, the acyl groups have two to four carbon atoms, the cycloalkyl groups have three to six carbon atoms and the halogen are of the following: fluoride, chloride, bromide, or iodide.

Preferably, Het is one of the following rings: pyrrolyl, pyridyl, pyrimidinyl, imidazolyl, thiazolyl, oxazolyl, thiazolyl, pyrazinyl, tetrazolyl, triazolyl. Each of these rings can possibly be substituted by one or more of the following: alkyl, phenyl

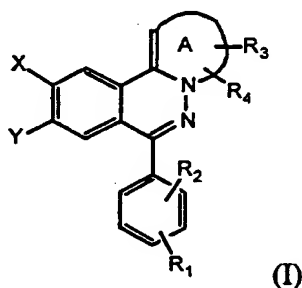
or phenylalkyl. The preferred substituents are methyl, phenyl or benzyl.

The compounds of the formula (I) in which R_7 is NO-alk, $C(COOR_{10})R_{20}$, $C(CONR_{10}R_{21})R_{20}$ or CHR_{19} can exist as isomers (E and Z). The compounds of the present invention include the isomers E and Z and their mixtures.

5 The compounds of the formula (I), in which R is $CH-R_6$ and R_6 is $-CO-COOR_{10}$, can exist as tautomers (E and Z). The compounds of the present invention include the tautomers E and Z and their mixtures.

The compounds of the present invention include the enantiomers and diastereoisomers of the compounds of the formula (I), in which R is $C(R_4)R_5$ or $CH-R_6$.

(25) Phthalazine derivatives (I) in DE 196 17 862 A1 as shown below:

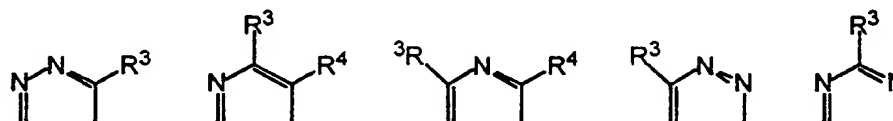


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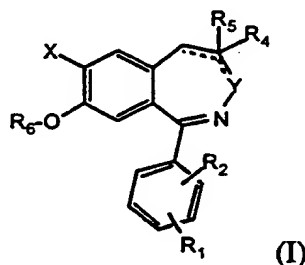
Phthalazine derivatives of the formula I wherein R^1 and R^2 are identical or different and hydrogen, C_1-C_6 -alkyl, nitro, halogen, the group $-NR^8R^9$, $-O-C_1-4$ -alkyl or CF_3 ; R^3 and R^4 are identical or different and hydrogen, an eventually substituted C_1-C_6 -alkyl-, aryl- or hetaryl residue or C_{3-7} -cycloalkyl; R^8 and R^9 are identical or different and hydrogen, C_1-C_6 -alkyl or the group $-CO-C_1-6$ -alkyl, X hydrogen; Y C_1-6 -alkoxy or X and Y together $-O-(CH_2)_n-O-$; n 1, 2 or 3 mean and A forms together with nitrogen a five-membered heterocycle, which can contain 1-3 nitrogen atoms, as well as its isomers and pharmaceutically acceptable salts thereof.

25 Under alkyl one has to understand a linear or branched alkyl residue as for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sek. butyl, pentyl, isopentyl

or hexyl, which can be substituted by C₁-C₆-alkoxy, halogen or C₁-C₆-alkonyl. If there is a halogenated alkyl residue present, then it can be multiple halogenated or perhalogenated such as CF₃. Under halogen one has to understand fluoride, chloride, bromide and iodide. The aryl- and hetaryl residue R³ and R⁴ can be single or multiple substituted with halogen, C₁₋₄-alkoxy or C₁₋₄-alkyl. The alyl residue can contain 6-10 carbon atoms whereby phenyl is preferred. One might mention as a hetaryl residue for example pyridinyl. With cycloalkyl one means cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, respectively, particularly C₃₋₅-cycloalkyl. Suitable as alkanoyl residues are aliphatic carbonic acid residues such as formyl, acetyl, propionyl, butanoyl, caproyl, valeroyl, trimethylacetyl and others. If A together with the nitrogen atom forms a 5-membered heterocycle, then is in position 4 an exocyclic double bond. Preferred are heteroaromatics with 1-3 nitrogen atoms, whereby for example A has the following meaning:

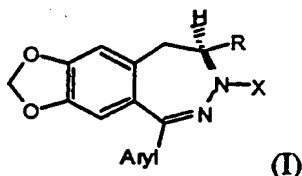


(26) 2,3-Benzodiazepine derivatives (I) in DE 196 04 920 A1 as shown below:



2,3-Benzodiazepine derivatives having general formula (I) wherein X is hydrogen or halogen, Y -NR³-or-N=, R¹ and R² are identical or different and hydrogen, C₁-C₆-alkyl, nitro, halogen, the group -NR⁸R⁹, -O-C₁₋₄-alkyl or -CF₃, R³ is hydrogen, the group -CO-R¹⁰, C₁₋₆-alkyl or C₃₋₇-cycloalkyl; R⁴ eventually substituted C₁-C₆-alkyl; R⁵ hydrogen or R⁴ and R⁵ together oxygen; R⁶ C₁₋₄-alkyl; R⁸ and R⁹ are identical or different and hydrogen, C₁-C₆-alkyl or -CO-C₁₋₆-alkyl; R¹⁰ hydrogen, eventually substituted C₁-C₆-alkyl, eventually substituted C₆₋₁₀-aryl, the group -NR¹¹R¹², -O-C₁₋₆-alkyl, C₃₋₇-cycloalkyl, C₂₋₆-alkenyl or -O-C₃₋₇-cycloalkyl; R¹¹ and R¹² are identical or different and hydrogen, eventually substituted C₁-C₆-alkyl or eventually substituted C₆₋₁₀-aryl and -C...C... a double bond or single bond means as well as their isomers and pharmaceutically acceptable salts thereof.

(27) Dihydro-2,3-benzodiazepine derivatives (I) in WO 96-06606 as shown below:

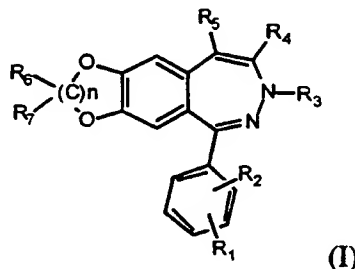


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Dihydro-2,3-benzodiazepine derivatives having general formula (I) wherein R is hydrogen or C₁-C₁₀ alkyl; X is an aromatic moiety selected from phenyl, thienyl, furyl, pyridyl, imidazolyl, benzimidazolyl, benzothiazolyl and phthalazinyl which is unsubstituted or substituted with one or more moieties chosen from the group consisting of halogen, hydroxy, cyano, nitro, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ alkoxy, carboxy, C₁-C₆ alkoxycarbonyl, acetyl, formyl, carboxymethyl, hydroxymethyl, amino, aminomethyl, methylenedioxy and trifluoromethyl; and "Aryl" represents p-nitrophenyl, p-aminophenyl or p-(protected amino) phenyl; or a pharmaceutically acceptable salt thereof.

25

(28) 3-Substituted 3H-2,3-benzodiazepine derivatives (I) in WO 96-04283 A1 as shown below:



(I)

3-Substituted 3H-2,3-benzodiazepine derivatives of general formula (I) wherein R¹ and R² are identical or different and hydrogen, C₁-C₆-alkyl, nitro, halogen, the group -NR⁸R⁹, -O-C₁₋₄-alkyl or CF₃; R³ the group -C=O

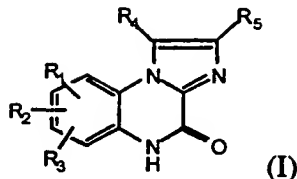


R⁴ eventually substituted C₁-C₆-alkyl; R⁵ hydrogen or eventually substituted C₁-C₆-alkyl; R⁶ and R⁷ are identical or different and hydrogen, eventually substituted C₁-C₆-alkyl or eventually substituted aryl; R⁸ and R⁹ are identical or different and hydrogen, C₁-C₆-alkyl or the group



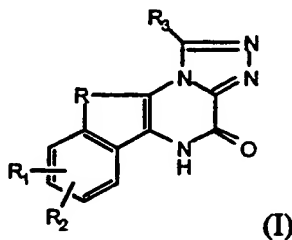
R¹⁰ hydrogen, eventually substituted C₁-C₆-alkyl, eventually substituted aryl, the group -NR¹¹R¹², -O-C₁₋₆-alkyl, C₃₋₇-cycloalkyl, C₂₋₆-alkenyl or -O-C₃₋₇-cycloalkyl; R¹¹ and R¹² are identical or different and hydrogen, eventually substituted C₁-C₆-alkyl or eventually substituted aryl; R¹³ C₁-C₆-alkyl and n stands for 1, 2 or 3; means as well as their isomers and pharmaceutically acceptable salts thereof.

(29) Heterocyclic compounds (I) in WO 95-21842 as shown in below:



- 5 Imidazol[1,2-a]quinoxalinone derivatives of general formula (I) wherein R^1 , R^2 , R^3 are the same or independently are H, alkyl, alkoxy, halogen, NO_2 , NH_2 , CF_3 , CN, SO_2CH_3 , SO_2CF_3 , $\text{SO}_2\text{NR}'\text{R}''$ or a 5- or 6- membered N- containing heterocyclic ring, optionally substituted, and R' , R'' are independently H or alkyl; and R^4 is H or $\text{CH}_2\text{-R}^6$; and R^6 is H, halogen, $\text{POR}''' \text{R}''''$, $\text{NR}^7 \text{R}^8$ or a 5- or 6-membered N-containing heterocyclic ring optionally substituted, and R''' , R'''' are independently hydroxy or alkoxy; and R^7 , R^8 are the same or independently are H, (a) or alkyl optionally substituted; and n is 1, 2, or 3; (b) CH_2OH , CHNOH , CN, (c) or (d) and R^9 is OH, alkoxy, H or $\text{NR}^{10} \text{R}^{11}$; and R^{10} , R^{11} are the same or independently are H, NH_2 or OH; and X is O or S; and Y is O, S or NH_2 , and pharmaceutically acceptable salts thereof.
- 10
- 15

(30) 1,2,4-Triazolo[4,3-a]pyrazine-4-one derivatives and their salts in WO 95-26351 as shown below:



20 1,2,4-Triazolo[4,3-a]pyrazine-4-one derivatives having general formula (I) wherein R is N-alk, $\text{C}(\text{R}_4)\text{R}_5$, CH-R_6 or C=R_7 . R_1 and R_2 are the same or different and are selected from the group consisting of hydrogen or halogen atoms or of alkyl, alkoxy,

amino, $-N=CH-N(alk)alk'$, nitro, cyano, phenyl, imidazolyl, SO_3H , hydroxy, polyfluoralkoxy, carboxy, alkoxycarbonyl, $-NH-CO-NR_{11}R_{12}$, $-N(alk)-CO-NR_{11}R_{12}$, $-N(alk-Ar)-CO-NR_{11}R_{12}$, $-NH-CS-NR_{11}R_{12}$, $-N(alk)-CS-NR_{11}R_{12}$, $-NH-CO-R_{11}$, $-NH-CS-R_{24}$, $-NH-C(=NR_{27})-NR_{10}R_{12}$, $-N(alk)-C(=NR_{27})-NR_{10}R_{12}$, $-Co-NR_{10}R_{12}$, $-NH-SO_2-NR_{10}R_{12}$, $N(alk)-SO_2-NR_{10}R_{12}$, $-NH-SO_2-CF_3$, $-NH-SO_2-alk$, $-NR_{10}R_{13}$, $S(O)_m-alk-Ar$, $-SO_2-NR_{10}R_{12}$, 2-oxo-1-imidazolidinyl in which position 3 may be substituted by an alkyl group, or 2-oxo-1-perhydropyrimidinyl in which position 3 may be substituted by an alkyl group, R_3 is hydrogen, alkyl, cycloalkyl, alkylcycloalkyl, phenylalkyl, phenyl, Het or amino, R_4 is alkyl, $-alk-Het$, or phenylalkyl in which the phenyl group is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, $-alk-NH_2$, $-COOR_{10}$, and $-alk-COOR_{10}$, R_5 is an alkyl group (the term C_1-C_{10} alkyl represents a straight or branched alkyl chain having one to ten carbon atoms), $-alk-Het$, $-NR_8R_9$, $-NH-CHO$, $-NH-COOR_{17}$, $-NH-SO_2-R_{24}$, $-COOR_{10}$, $-alk-COOR_{10}$, $-alk-CONR_{10}R_{18}$, $-alk-NR_{10}R_{18}$, $-alk-OH$, $-alk-CN$, phenylalkyl in which the phenyl group is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, $-alk-NH_2$, $-COOR_{10}$, and $-alk-COOR_{10}$, $-NH-CO-Ar$ in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, $-alk-NH_2$, $-COOR_{10}$, and $-alk-COOR_{10}$, $-NH-CO-Het$, $-NH-CO-alk-Het$, $-NH-CO-alk-COOR_{10}$, $-NH-CO-alk-NR_{10}R_{18}$, $-NH-CO-alk-Ar$ in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, $-alk-NH_2$, $-COOR_{10}$, and $-alk-COOR_{10}$, pyrrolyl-1 which may be substituted by $-COOR_{10}$, $-NH-CO-NH-alk-Ar$ in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, $-alk-NH_2$, $-COOR_{10}$, and $-alk-COOR_{10}$, $-NH-CO-NH-Het$, $-NH-CO-NH-alk-Het$, $-NH-CO-NH-Ar$ in which Ar may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, $-alk-NH_2$, $-COOR_{10}$, and $-alk-COOR_{10}$, $-NH-CO-alk$, $-NH-CO-cycloalkyl$, $-NH-CO-NH-alk$ or $-NH-CO-NH_2$, or R_4 and R_5 , together with the carbon atom they attached to, are a cycloalkyl group, R_6 is hydrogen, hydroxy, alkyl (the term C_1-C_{10} alkyl represents a straight or branched alkyl chain having one to ten carbon atoms), $-alk-OH$, $-NR_{14}R_{15}$,

-alk-NR₁₄R₁₅, -alk-Het, -NH-CHO, -COO-alk, -alk -COOR₁₀, -alk-CO-NR₁₀R₁₈,
 -phenylalkyl in which the phenyl group may be substituted by one or more of the
 following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₁₀,
 and -alk-COOR₁₀, R₁₆-COOR₁₀, -CO-COOR₁₀ or pyrrolyl-1 possibly substituted by
 5 -COOR₁₀.

R₇ is oxygen, or NOH, NO-alk-COOR₁₀, NO-alk, CHR₁₉, NR₁₀, C(COOR₁₀) or
 C(CONR₁₀R₂₁)R₂₀, R₈ is hydrogen, alkyl, -alk-COOR₁₀, -alk-NR₁₀R₂₁, -alk-Het or
 phenylalkyl in which the phenyl group may be substituted by one or more of the
 following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₁₀,
 10 and -alk-COOR₁₀, R₉ is hydrogen or alkyl, R₁₀ is hydrogen or alkyl, R₁₁ is hydrogen,
 alkyl, (the term C₁-C₉ alkyl represents a straight or branched alkyl chain having one to
 nine carbon atoms), alkoxy, -alk-COOR₁₀, -alk-Het, -alk-NR₁₂R₁₀, phenylalkyl in
 which the phenyl group may be substituted by one or more of the following: halogen,
 alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, carboxy, alkoxycarbonyl, cyano, and
 15 -alk-COOR₁₀, phenyl in which the phenyl group may be substituted by one or more of
 the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, carboxy,
 alkoxycarbonyl, cyano and -alk-COOR₁₀ or-Het, R₁₂ is hydrogen or alkyl, R₁₃ is alkyl,
 Het or alkoxycarbonyl, R₁₄ and R₁₅ are the same or different and are each an alkyl
 moiety, or R₁₄ is hydrogen and R₁₅ is hydrogen, alkyl, -COR₂₂, -CSR₂₃ or -SO₂R₂₄, R₁₆
 20 is a -CHOH- chain or -CH(OH)-alk(C₁-C₅), R₁₇ is alkyl or phenylalkyl, R₁₈ is
 hydrogen or alkyl, R₁₉ is hydroxy, alkyl, -alk-Het, -NR₂₅R₂₆, -alk-COOR₁₀, -Het,
 -phenyl in which the phenyl group may be substituted by one or more of the
 following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, -COOR₁₀, cyano,
 and -alk-COOR₁₀, phenylalkyl in which the phenyl group may be substituted by one or
 25 more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂,
 -COOR₁₀, cyano and -alk-COOR₁₀, R₂₀ is hydrogen or alkyl, R₂₁ is hydrogen or alkyl,
 R₂₂ is alkyl, cycloalkyl, -COOalk, -alk-COOR₁₀, phenyl in which the phenyl group
 may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro,
 amino, hydroxy, -alk-NH₂, -COOR₁₀, cyano and -alk-COOR₁₀, phenylalkyl in which
 30 the phenyl group may be substituted by one or more of the following: halogen, alkyl,

alkoxy, nitro, amino, hydroxy, -alk-NH₂, -COOR₁₀, cyano and -alk-COOR₁₀, -alk-NR₁₀R₁₂, -NH-Ar in which Ar may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, -COOR₁₀, cyano and -alk-COOR₁₀, phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, -COOR₁₀, cyano and -alk-COOR₁₀, -Het, -alk-Het, -OR₁₇, -NH-alk-Ar in which Ar may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, -COOR₁₀, cyano and -alk-COOR₁₀, -NH-alk-Het, -NH-alk, -NH₂ or -NH-Het, R₂₃ is -NH-alk, -NH-Ar, -NH-Het or -NH₂, R₂₄ is alkyl or phenyl, R₂₅ and R₂₆ are the same or different and are each alkyl or cycloalkyl, R₂₇ is hydrogen or alkyl.

The term alk refers to an alkyl or alkylene moiety. The term alk' refers to an alkyl moiety. m = 0, 1 or 2. The term Ar refers to a phenyl moiety. The term Het refers to a heterocycle which is mono- or poly- saturated or unsaturated with one to nine carbon atoms and one or more heteroatom (O, S, N) which may be substituted with one or more of the following: alkyl, phenyl, or phenylalkyl.

Unless otherwise stated, in the above and below definitions, the alkyl, alkylene or alkoxy moieties are a straight or branched chain having one to six carbon atom, the acyl moieties have two to four carbon atoms, the cycloalkyl moieties have three to six carbon atoms and the halogen atoms are selected from the following: fluoride, chloride, bromide or iodide.

Preferably, Het is one of the following rings: pyrrolyl, pyridyl, pyrimidinyl, imidazolyl, thiazolyl, oxazolynyl, thiazolynyl, pyrazinyl, tetrazolyl, triazolyl, pyrrolidinyl, piperazinyl, thienyl, furyl, azetidynyl and imidazolynyl. Each of these rings may be substituted by one or more of the following: alkyl, phenyl or phenylalkyl. The preferred substituents are methyl, phenyl or benzyl.

The preferred polyfluoroalkoxy groups are the trifluoromethoxy groups.

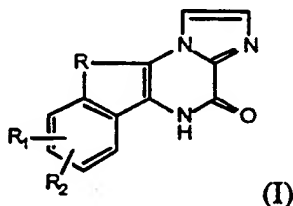
The compounds of the formula (I) in which R₇ is NO-alk, C(COOR₁₀)R₂₀, C(CONR₁₀R₂₁)R₂₀ or CHR₁₉, can exist as isomers (E and Z). The compounds of the present invention include the isomers E and Z and their mixtures.

The compounds of the formula (I), in which R is CH-R₆ and R₆ is -CO-

COOR₁₀, can exist as tautomers (E and Z). The compounds of the present invention include the tautomers E and Z and their mixtures.

The compounds of the present invention include the enantiomers and diastereoisomers of the compounds of the formula (I), in which R is C(R₄)R₅ or CH-R₆.

(31) Imidazo(1,2-a)indeno(1,2-e)pyrazin-4-one derivatives and their salts in WO 95-26350 as shown below:



Imidazo(1,2-a)indeno(1,2-e)pyrazin-4-one derivatives having general formula (I) wherein R is C=R₃, C(R₄)R₅ or CH-R₆, R₁ and R₂ are the same or different and are selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, amino, -N=CH-N(alk)alk', nitro, cyano, phenyl, imidazolyl, SO₃H, hydroxy, polyfluoralkoxy, -COOR₇, -NH-CO-NR₈R₉, -N(alk)-CO-NR₈R₉, -N(alk-Ar)-CO-NR₈R₉, -NH-CS-NR₈R₉, -N(alk)-CS-NR₈R₉, -NH-CO-NR₁₈, -NH-CS-R₁₉, -NH-C(=NR₂₀)-NR₇R₉, -N(alk)-C(=NR₂₀)-NR₇R₉, -NH-SO₂-NR₇R₉, N(alk)-SO₂-NR₇R₉, -CO-NR₇R₉, -NH-SO₂-CF₃, -NH-SO₂-alk, -NR₉R₁₁, S(O)_m-alk-Ar, -SO₂-NR₇R₉, 2-oxo-1-imidazolidinyl in which position 3 may be substituted by an alkyl group, or 2-oxo-1-perhydropyrimidinyl in which position 3 may be substituted by an alkyl group, R₃ is NO-alk, CHR₁₀, NR₇, C(COOR₇)R₁₆ or C(CONR₇R₁₅)R₁₆, R₄ is alkyl, -alk-Het, -alk-Het" or phenylalkyl in which the phenyl group is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₇ and -alk-COOR₇, R₅ is -NR₁₂R₁₃, -NH-CHO, -NH-CHO, -NH-COOR₁₇, -NH-SO₂R₁₉,

- COOR₇, -alk-COOR₇, -alk-CONR₇R₁₅, -alk-NR₇R₁₅, -alk-OH, -alk-CN, -alk-Het", phenylalkyl in which the phenyl group is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₇ and -alk-COOR₇, -NH-CO-Ar in which Ar is substituted by one or more of the following:
- 5 halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₇ and -alk-COOR₇, -NH-CO-Het, -NH-CO-Het", -NH-CO-alk-Het, -NH-CO-alk-Het", -NH-CO-alk-COOR₇, -NH-CO-alk-NR₇R₁₅, -NH-CO-alk-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₇, and -alk-COOR₇, -NH-CO-C(Ar)(CF₃)OCH₃, pyrrolyl-1 which may be
- 10 substituted by -COOR₇, -NH-CO-NH-alk-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₇, and -alk-COOR₇, -NH-CO-NH-Het, -NH-CO-NH-Het", -NH-CO-NH-alk-Het, -NH-CO-NH-alk-Het", -NH-CO-NH-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂,
- 15 -COOR₇, and -alk-COOR₇, -NH-COalk, -NH-COcycloalkyl, -NH-CO-NH-alk or -NH-CO-NH₂, R₆ is -NH-CHO, -COOalk, -alk-COOR₇, -alk-CO-NR₇R₁₅, phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₇, and -alk-COOR₇, -R₁₄-COOR₇, -CO-COOR₇, -NH-COOR₁₇, -NH-CO-Ar in which Ar is substituted by
- 20 one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₇, and -alk-COOR₇, -NH-CO-Het, -NH-CO-alk-Het, -NH-CO-Het", -NH-CO-alk-Het", -NH-CO-alk(C₂-C₆)-COOR₇, -NH-CO-alk(C₂-C₆)-NH₂, -NH-CO-alk-N(alk)₂, -NH-CO-alk-NHalk, -NH-CO-alk-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂,
- 25 -COOR₇, and -alk-COOR₇, -NH-CO-C(Ar)(CF₃)OCH₃, -alk-Het", pyrrolyl-1 may be substituted by -COOR₇, -NH-CO-NH-alk-Ar in which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₇, and -alk-COOR₇, -NH-CO-NH-alk-Het, -NH-CO-NH-alk-Het", -NH-CO-NH-Het", or -NH-CO-NH-Ar in which Ar is substituted by one or more of the
- 30 following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₇,

and -alk-COOR₇, R₇ is hydrogen or alkyl, R₈ is hydrogen, alkyl, -alk-COOR₇, -alk-Het", -alk-Het, -alk-NR₉R₇ or phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, -COOR₇, cyano, -alk-COOR₇, or phenyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, -COOR₇, cyano, -alk-COOR₇, -Het or -Het", R₉ is hydrogen or alkyl, R₁₀ is -alk-COOR₇, -Het", -alk-Het", phenyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, COOR₇, cyano, -alk -COOR₇, or phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, -COOR₇, cyano, -alk--COOR₇, R₁₁ is alkyl, -Het, -Het" or alkylcarbonyl, R₁₂ is hydrogen, alkyl, -alk-COOR₇, -alk-NR₇R₁₅, -alk-Het, -alk-Het", or phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, carboxy, alkoxy carbonyl, cyano, and -alk-COOR₇, R₁₃ is hydrogen or alkyl, R₁₄ is a -CHOH- or -CHOH-alk(C₁-C₅) chain, R₁₅ is hydrogen or alkyl, R₁₆ is hydrogen or alkyl, R₁₇ is alkyl or phenylalkyl, R₁₈ is hydrogen, or an alkyl moiety (the term C₁-C₉ alkyl represents a straight or branched alkyl chain having one to nine carbon atoms), alkoxy, -alk-COOR₇, -alk-Het", -alk-Het, , -alk-NR₉R₇, phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, -COOR₇, cyano and -alk-COOR₇, phenyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, cyano, -alk-COOR₇, Het or Het", R₁₉ is alkyl or phenyl, R₂₀ is hydrogen or alkyl.

The term alk refers to an alkyl or alkylene moiety. The term alk' refers to an alkyl moiety. The term Ar refers to a phenyl moiety. m = 0,1 or 2. The term Het refers to a heterocycle which is mono- or poly-saturated or unsaturated with four to nine carbon atoms and one or more heteroatom (O, S, N). The term Het" refers to a heterocycle which is mono- or poly-saturated or unsaturated with one to three carbon atoms and one or more heteroatom (O, S, N) may be substituted with one or - or poly-

saturated or insaturated with four to nine carbon atoms and one or more heteroatom (O, S, N) may be substituted with one or more of the following: alkyl, phenyl, or phenylalkyl. Provided that when R_1 and R_2 are hydrogen, R is CHR_6 , R_6 is alk-Het" in which alk is alkyl (C_1) and Het" is not 2-imidazol.

5 Unless otherwise stated, in the above and below definitions, the alkyl or alkylene moieties are a straight or branched chain having one to six carbon atom, the cycloalkyl moieties have three to six carbon atoms and the halogen atoms are selected from the following: fluoride, chloride, bromide, or iodide.

10 Preferably, Het is one of the following cycles: pyrrolyl, pyridyl, pyrimidinyl, morpholinyl, pyrazinyl, pyrrolidinyl, piperazinyl, piperidinyl, thienyl and furyl. Het" is one of the following: pyrrolyl, pyridyl, pyrimidinyl, imidazolyl, thiazolyl, thiazolinyl, pyrazinyl, tetrazolyl, triazolyl, oxazolyl, pyrrolidinyl, azetidyl, piperazinyl, piperidinyl, thienyl, oxazolinyl, furyl and imidazolinyl. Each of these rings may be substituted by one or more of the following: alkyl, phenyl or phenylalkyl.

15 The preferred substituents are methyl, phenyl or benzyl.

The preferred polyfluoroalkoxy groups are the trifluoromethoxy groups. The compounds of the formula (I) in which R_3 is NO-alk, $C(COOR_7)R_{16}$, $C(CONR_7R_{15})R_{16}$ or CHR_{10} can exist as isomers (E and Z). The compounds of the present invention include the isomers E and Z and their mixtures.

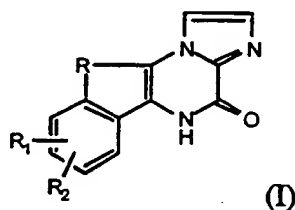
20 The compounds of the formula (I), in which R is $CH-R_6$ and R_6 is $-CO-COOR_7$, can exist as tautomers (E and Z). The compounds of the present invention include the tautomers E and Z and their mixtures.

25 The compounds of the present invention include the enantiomers and diastereoisomers of the compounds of the formula (I), in which R is $C(R_4)R_5$ or $CH-R_6$.

30 The compounds of the present invention include compounds of the formula (I) in which R , R_1 and R_2 are as defined previously except for when: a) R_1 and R_2 are hydrogen, R is CHR_6 , R_6 is -alk-Het" in which alk is an alkyl moiety (C_1) and Het" is a 2-imidazolyl moiety, b) R_1 and R_2 are hydrogen, R is CHR_6 , R_6 is $-NHCHO$ or $alk-COOR_7$ in which R_7 is hydrogen or a tertbutyl group, c) R_1 and R_2 are hydrogen, R is

$C=R_3$, R_3 is CHR_{10} and R_{10} is a 2-imidazolyl moiety, d) R_1 is hydrogen, R_2 is CHR_6 and R_6 is $-NHCHO$. The preferred compounds are those with R_1 in position -7 or -8.

- 5 (32) Indeno[1,2-e]pyrazine-4-one (I) in WO 95-26349 as shown below:

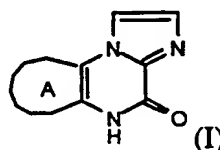


- Indeno[1,2-e]pyrazine-4-one of formula (I), wherein R is a substituted nitrogen, oxygen or sulphur atom or a radical $C=R_3$, $C(R_4)R_5$ or $CH-R_6$; R_1 is a hydroxy radical, polyfluoroalkoxy, carboxy, alkoxycarbonyl, $-NH-CHO$ or $-NH-CO-N(alk)Ar$ where Ar is optionally substituted, $-N(alk)-CO-NR_8R_9$, $-N(alk-Ar)-CO-NR_8R_9$, $-NH-CO-NR_9R_{12}$, $-NH-CS-NR_8R_9$, $-N(alk)-CS-NR_8R_9$, $-NH-CO-R_{10}$, $-NH-CS-R_{20}$, $-NH-C(=NR_{21})-NR_7R_9$, $-N(alk)-C(=NR_{21})-NR_7R_9$, $-NH-SO_2-NR_7R_9$, $N(alk)-SO_2-NR^7R^9$, $-CO-NR_7R_9$, $-NH-SO_2-CF_0$, $-NH-SO_2-alk$, $-NR_9R_{11}$, $-S(O)_m-alk-Ar$, $-SO_2-NR_7R_9$, optionally 3-substituted 2-oxo-1 imidazolidinyl or optionally 3-substituted 2-oxo-1 perhydropyrimidinyl; R_2 is a hydrogen or halogen atom or an alkyl radical, alkoxy, amino, $-NH-CO-NH-Ar$, $N=CH.N(alk)alk'$, nitro, cyano, phenyl, imidazolyl, acylamino, SO_3H , hydroxy, polyfluoroalkoxy, carboxy, alkoxycarbonyl, $-NH-CHO$, $-NH-CO-N(alk)Ar$ where Ar is optionally substituted, $-N(alk)-CO-NR_8R_9$, $-N(alk-Ar)-CO-NR_8R_9$, $-NH-CO-NR_9R_{12}$, $-NH-CS-NR_8R_9$, $-N(alk)-CS-NR_8R_9$, $-NH-CO-R_{10}$, $-NH-CS-R_{20}$, $-NH-C(=NR_{21})-NR_7R_9$, $-N(alk)-C(=NR_{21})-NR_7R_9$, $-NH-SO_2-NR_7R_9$, $-N(alk)-SO_2-NR_7R_9$, $-CO-NR_7R_9$, $-NH-SO_2-CF_3$, $-NH-SO_2-alk$, $-NR_9R_{11}$, $-S(O)_m-alk-Ar$, $-SO_2-NR_7R_9$, optionally 3-substituted 2-oxo-1-imidazolidinyl or optionally 3-substituted 2-oxo-1-perhydropyrimidinyl; R_3 is an oxygen atom or a NOH , $NO-alk-COOX$ or $CH-R_{13}$ radical, R^4 is an alkyl radical; $-alk-Het$ or $-alk-Ar$; R_5 is a straight or branched C_{1-11}

alkyl radical, -alk-Het or -alk-Ar, or R_4 and R_5 , taken together with the carbon atom to which they are attached, form a cycloalkyl radical; R_6 is a hydrogen atom radical or a hydroxy radical, straight or branched C_{1-11} alkyl, $-NR_{14}R_{15}$, -alk-OH, -alk- $NR_{14}R_{15}$, -alk-Ar or -alk-Het; and salts thereof.

5

(33) Imidazo[1,2-a]pyrazine-4-one derivatives (I) in WO95-26352 as shown below:

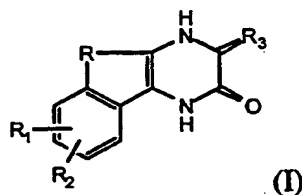


10

Compounds of formula (I), wherein ring A is selected from rings 1, 2 and 3, wherein R is a CH_2 radical or a sulphur, oxygen or nitrogen atom substituted by an alkyl radical, and salts thereof.

15

(34) 5H-Indeno[1,2-b]pyrazine-2,3-dione derivatives and their salts (I) in WO 95-26342 as shown below:



20

5H-Indeno[1,2-b]pyrazine-2,3-dione of formula (I), wherein R is N-alk, $C(R_4)R_5$, $CH-R_6$ or $C=R_7$, R_1 and R_2 are the same or different and are selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, amino, $-N=CH-N(alk)alk'$, nitro, cyano, phenyl, imidazolyl, SO_3H , hydroxy, polyfluoralkoxy, carboxy, alkylcarbonyl, $-NH-CO-NR_{11}R_{12}$, $-N(alk)-CO-NR_{11}R_{12}$, $-N(alk-Ar)-CO-NR_{11}R_{12}$, $-NH-CS-NR_{11}R_{12}$,

-N(alk)-CS-NR₁₁R₁₂, -NH-CO-NR₁₁, -NH-CS-R₂₄, -NH-C(=NR₂₇)-NR₁₀R₁₂, -N(alk)
 C(=NR₂₇)-NR₁₀R₁₂, -CO-NR₁₀R₁₂, -NH-SO₂-NR₁₀R₁₂, N(alk)-SO₂-NR₁₀R₁₂, -NH-
 SO₂-CF₃, -NH-SO₂-alk, -NR₁₀R₁₃, S(O)_m-alk-Ar, -SO₂-NR₁₀R₁₂, 2-oxo-1-
 5 imidazolidinyl in which position 3 may be substituted by an alkyl group, or 2-oxo-1-
 perhydropyrimidinyl in which position 3 may be substituted by an alkyl group, R₃ is
 oxygen, NOH, NOalk or NOalkAr, R₄ is alkyl, -alk-Het or phenylalkyl in which the
 phenyl group is substituted by one or more of the following: halogen, alkyl, alkoxy,
 nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₁₀, and -alk-COOR₁₀, R₅ is an alkyl
 10 group (the term C₁-C₁₁ alkyl represents a straight or branched alkyl chain having one
 to eleven carbon atoms), -alk-Het, NR₈R₉, -NH-CHO, -NH-COOR₁₇, -NH-SO₂R₂₄,
 -COOR₁₀, -alk-COOR₁₀, -alk-CONR₁₀R₁₈, -alk-NR₁₀R₁₈, -alk-OH, -alk-CN,
 phenylalkyl in which the phenyl group is substituted by one or more of the following:
 halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₁₀, and -alk-
 COOR₁₀, -NH-CO-Ar in which Ar is substituted by one or more of the following:
 15 halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₁₀, and -alk-
 COOR₁₀, -NH-CO-Het, -NH-CO-alk-Het, -NH-CO-alk-COOR₁₀, -NH-CO-alk-
 NR₁₀R₁₈, -NH-CO-alk-Ar in which Ar is substituted by one or more of the following:
 halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₁₀, and -alk-
 COOR₁₀, pyrrolyl-1 which may be substituted by -COOR₁₀, -NH-CO-NH-alk-Ar in
 20 which Ar is substituted by one or more of the following: halogen, alkyl, alkoxy, nitro,
 amino, hydroxy, cyano, -alk-NH₂, -COOR₁₀, and -alk-COOR₁₀, -NH-CO-NH-Het,
 -NH-CO-NH-alk-Het, -NH-CO-NH-Ar in which Ar is substituted by one or more of
 the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂,
 -COOR₁₀, and -alk-COOR₁₀, -NH-COalk, -NH-CO-cycloalkyl, -NH-CO-NH-alk or
 25 -NH-CO-NH₂, or R₄ and R₅, together with the carbon atom they attached to, are a
 cycloalkyl group, R₆ is hydrogen, hydroxy, alkyl (the term C₁-C₁₁ alkyl represents a
 straight or branched alkyl chain having one to eleven carbon atoms), -alk-OH,
 -NR₁₄R₁₅, -alk-NR₁₄R₁₅, alk-Het, -NH-CHO, -COOalk, -alk-COOR₁₀, -alk-CO-
 NR₁₀R₁₈, phenylalkyl in which the phenyl group may be substituted by one or more of
 30 the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂,

-COOR₁₀, and -alk-COOR₁₀, -R₁₆-COOR₁₀, -CO-COOR₁₀ or pyrrolyl-1 may be substituted by -COOR₁₀, R₇ is oxygen or NOH, NO-alk-COOR₁₀, NO-alk, CHR₁₉, C(COOR₁₀)R₂₀ or C(CONR₁₀R₂₁)R₂₀, R₈ is hydrogen, alkyl, -alk-COOR₁₀, -alk-NR₁₀R₂₁, -alk-Het or phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, cyano, -alk-NH₂, -COOR₁₀ and -alk-COOR₁₀, R₉ is hydrogen or alkyl, R₁₀ is hydrogen or alkyl, R₁₁ is hydrogen, alkyl (the term C₁-C₉ alkyl represents a straight or branched alkyl chain having one to nine carbon atoms), alkoxy, -alk-COOR₁₀, alk-Het, -alk-NR₁₂R₁₀, phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, carboxy, alkoxy carbonyl, cyano and -alk-COOR₁₀, phenyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, carboxy, alkoxy carbonyl, cyano and -alk-COOR₁₀ or -Het, R₁₂ is hydrogen or alkyl, R₁₃ is alkyl, Het or alkoxy carbonyl, R₁₄ and R₁₅ are the same or different and are each an alkyl group or R₁₄ is hydrogen and R₁₅ is hydrogen, alkyl, -COR₂₂, -CSR₂₃ or SO₂R₂₄, R₁₆ is a -CHOH or -CH(OH)alk(C₁-C₅) chain, R₁₇ is alkyl or phenylalkyl, R₁₈ is hydrogen or alkyl, R₁₉ is hydroxy, alkyl, alk-Het, -NR₂₅R₂₆, -alk-COOR₁₀, -Het, phenyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, -COOR₁₀, cyano, and -alk-COOR₁₀ or phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, -COOR₁₀, cyano, and -alk-COOR₁₀, R₂₀ is hydrogen or alkyl, R₂₁ is hydrogen or alkyl, R₂₂ is alkyl, cycloalkyl, -COOalk, -alk-COOR₁₀, phenyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, -COOR₁₀, cyano, and -alk-COOR₁₀, phenylalkyl in which the phenyl group may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, -COOR₁₀, cyano, and -alk-COOR₁₀, -alk-NR₁₀R₁₂, -NH-Ar in which Ar may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, -COOR₁₀, cyano, and -alk-COOR₁₀, -phenylalkyl in which the phenyl group may be

substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, -COOR₁₀, cyano, and -alk-COOR₁₀, -Het, -alk-Het, -OR₁₇, -NH-alk-Ar in which Ar may be substituted by one or more of the following: halogen, alkyl, alkoxy, nitro, amino, hydroxy, -alk-NH₂, -COOR₁₀, cyano and -alk-COOR₁₀,
 5 NH-alk-Het, -NH-alk, -NH₂ or -NH-Het, R₂₃ is -NH-alk, -NH-Ar, -NH-Het or -NH₂, R₂₄ is alkyl or phenyl, R₂₅ and R₂₆ are the same or different and are each alkyl or cycloalkyl, R₂₇ is hydrogen or alkyl.

The term alk refers to an alkyl or alkylene group. The term alk' refers to an alkyl group. m = 0,1 or 2. The term Ar refers to a phenyl group. The term Het refers to
 10 a heterocycle which is mono or poly saturated or unsaturated with four to nine carbon atoms and one or more heteroatom (O, S, N) may be substituted with one or more of the following: alkyl, phenyl, or phenylalkyl. Provided that when R₁ and R₂ are hydrogen and R₃ is oxygen, R is not (a) C=R₇ in which R₇ is oxygen or NOH, (b) CH-R₆ in which R₆ is hydroxy.

15 Unless otherwise stated, in the above and below definitions, the alkyl or alkylene groups are a straight or branched alkyl chain having one to six carbon atom, the acyl groups have two to four carbon atoms, the cycloalkyl groups have three to six carbon atoms and the halogen are of the following: fluoride, chloride, bromide, or iodide.

20 Preferably, Het is one of the following rings: pyrrolyl, pyridyl, pyrimidinyl, thiazolyl, oxazoliny, thiazoliny, pyrazinyl, tetrazolyl, triazolyl, pyrrolidinyl, piperazinyl, piperidinyl, thienyl, furyl, azetidiny, imidazoliny. Each of these rings may be substituted by one or more of the following: alkyl, phenyl or phenylalkyl. The preferred substituents are methyl, phenyl or benzyl.

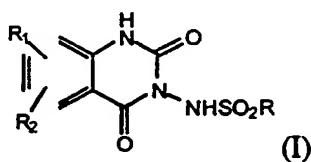
25 The preferred polyfluoroalkoxy groups are the trifluoromethoxy groups. The compounds of the formula (I) in which R is C=R₇, with R₇ being NO-alk, C(COOR₁₀)R₂₀, C(CONR₁₀R₂₁)R₂₀ or CHR₁₉ and/or with R₃ being NOH, NOalk or NOalkAr, can exist as isomers (E and Z). The compounds of the present invention include the isomers E and Z and their mixtures.

30 The compounds of the formula (I), in which R is CH-R₆ and R₆ is -CO-

COOR₁₀, can exist as tautomers (E and Z). The compounds of the present invention include the tautomers E and Z and their mixtures. The compounds of the present invention include the enantiomers and diastereoisomers of the compounds of the formula (I), in which R is C(R₄)R₅ or CH-R₆.

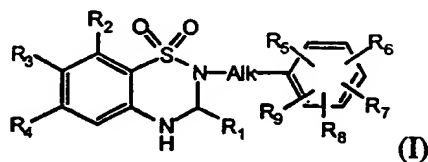
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(35) Quinazoline-2,4-dione (I) in WO 95-19346 as shown below:



- 10 Compounds of formula I wherein R is (C₁₋₆) alkyl or phenyl optionally mono-, di- or trisubstituted by halogen, (C₁₋₄)alkyl, (C₁₋₄)alkoxy, nitro, trifluoromethyl, amino, (C₁₋₄)alkylamino, di(C₁₋₄)alkylamino, cyano, (C₁₋₄)alkylsulfonyl, phenylsulfonyl or sulfonylamino, R₁ and R₂ independently are hydrogen, hydroxy, (C₁₋₄)alkyl, (C₁₋₄)alkoxy, (C₂₋₅)alkenyl, halogen, trifluoromethyl, nitro, amino, (C₁₋₄)alkylamino,
- 15 benzyloxy, benzoylamino, carboxy, cyano, (C₁₋₄)alkoxy-carbonyl, (C₁₋₄)alkylsulfonyl, phenylsulfonyl, sulfonylamino, (C₂₋₅)alkanoylamino or phenyl optionally substituted by (C₁₋₄)alkyl, halogen or nitro, provided that R₁ and R₂ are not both hydrogen if R is unsubstituted phenyl, or R₁ and R₂ on adjacent carbon atoms together form a group -CH=CH-CH=CH-, or a salt thereof. Alkyl and alkoxy groups and moieties in the
- 20 compounds of formula I may be straight - or branched-chained. Halogen means fluorine, chlorine, bromine or iodine. The compounds of formula I may form cationic salts, e.g. alkali metal or ammonium salts deriving from the sulfonamido group or when a carboxyl group is present. Depending on the nature of the substituents defined above, the compounds of formula I may also form acid addition salts. The tautomeric
- 25 forms of the compounds of formula I are also embraced.

(36) 3,4-Dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide-3-carboxylic acid derivatives (I) in WO 95-07899 as shown in below:

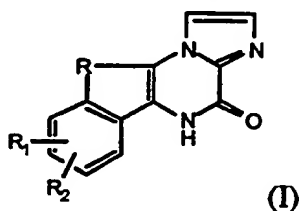


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Compounds of formula (I) wherein R₁ is a carboxy, alkoxycarbonyl, tetrazolyl, -CO-NH₂, -CO-NH-alk, -CO-N(alk)₂, -CO-NHOH, -CO-N(alk)OH, -CO-NH-O-R₁₀, -CO-N(alk)-OR₁₀ radical or a group convertible in vivo into a carboxy radical, R₂, R₃ and R₄, which are the same or different, are hydrogen or halogen atoms or alkyl or alkoxy radicals, R₅ is a hydroxy, -NHOH, -NH-CO-NH₂, -CH₂-NH₂, hydroxyalkyl, alkoxyalkyl, or -alk=NOH radical, R₆, R₇, R₈ and R₉, which are the same or different, are hydrogen or halogen atoms or alkyl, alkoxy, polyfluoroalkyl, amino, nitro, cyano, vinyl, polyfluoroalkoxy, alkoxycarbonyl, carboxy, phenylalkyloxy, phenylalkyl, benzoylamino, phenylcarbonyl, hydroxy, -NHOH, -NH-CO-NH₂, -CH₂-NH₂, hydroxyalkyl, alkoxyalkyl, -alk=NOH or phenoxy, with the phenyl ring being optionally substituted by one or several substituents selected from the halogen atoms and the alkyl, alkoxy or polyfluoroalkyl radicals, R₁₀ is an alkyl or phenylalkyl radical and alk is an alkyl or alkylene radical. The invention also concerns the salts of thereof, the preparation thereof, and drugs containing same.

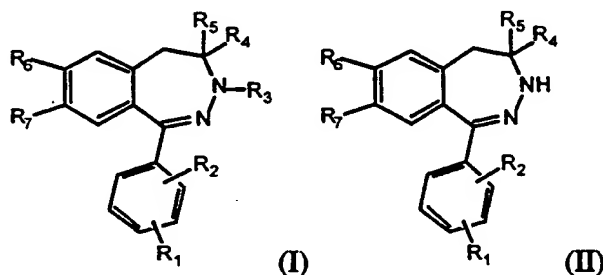
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(37) Imidazo(1,2-a)pyrazin-4-one derivatives (I) in WO95-02602 as shown below.



Compounds of formula (I), wherein R is an oxygen or sulphur atom or an NH or N-alk radical, and each of R₁ and R₂, which are the same or different, is a hydrogen or halogen atom or an alkyl, alkoxy, amino, acylamino, -NH-CO-NH-Ar, -N=CH-N(alk)alk', nitro, cyano, phenyl, imidazolyl or SO₃H radical, the preparation thereof, and drugs containing such compounds.

(38) 2,3-Benzodiazepine derivatives (I) and (II) in GB 2 311 779 A as shown below.

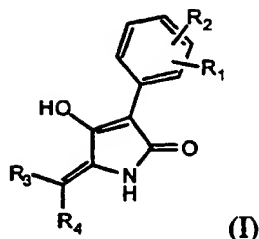


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Non-competitive AMPA antagonistic compounds of the formula I, wherein R¹ and R² represent, independently, a hydrogen, a halo, a C₁₋₄ alkyl group, a C₁₋₄ alkoxy group, a nitro group, a trifluoromethyl group or a group of the formula -NR⁸R⁹, wherein R⁸ and R⁹ stand, independently, for a hydrogen, a C₁₋₄ alkyl group or a group of the formula -COR¹⁰, wherein R¹⁰ is a hydrogen, a C₁₋₆ alkyl group that can be substituted, a C₆₋₁₀ aryl group, a C₁₋₄ alkoxy group, a C₃₋₅ cycloalkyl group, a C₂₋₆ alkenyl group a C₃₋₅ cycloalkoxy group or a group of the formula -NR¹¹R¹², wherein R¹¹ and R¹² mean, independently, a hydrogen, a C₁₋₄ alkyl group, a C₃₋₅ cycloalkyl group or a C₆₋₁₀ aryl group, R³ represents a C₁₋₄ alkyl groups a C₃₋₅ cycloalkyl group or a group of the formula -CO-R¹³, wherein R¹³ has the same definitions given in relation to R¹⁰, R⁴ and R⁵ mean, independently, a hydrogen or a C₁₋₃ alkyl group, R⁶ and R⁷ are, independently, a hydrogen, a chloro or a bromo, with the provision that if one of R⁶ and R⁷ stands for a hydrogen, the other is different from hydrogen, as well as the isomers thereof and the acid addition salts of the compounds or the isomers.

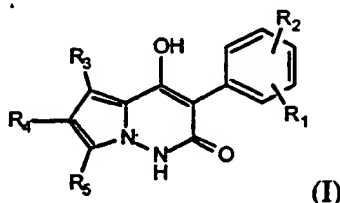
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(39) Tetramic acid derivatives (I) in GB 2 266 888 A as shown below:



Wherein R^1 and R^2 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$; or R^1 and R^2 together represent the residue of a carbocyclic or heterocyclic ring; R^3 and R^4 independently represent hydrogen, hydrocarbon, a heterocyclic group, trifluoromethyl, $-OR^c$, $-SR^c$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$, provided that R^3 does not represent C_{2-5} alkoxy carbonyl when R^4 represents an optionally substituted phenyl group; R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group; and R^c represents hydrocarbon or a heterocyclic group.

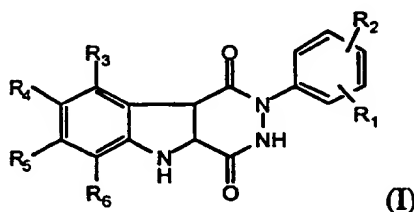
(40) Pyrrolo-pyridazinone derivatives (I) in GB 2 265 372 A as shown below:



Pyrrolo-pyridazinone derivatives, wherein R^1 and R^2 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$; or R^1 and R^2 together represent the residue of a carbocyclic or heterocyclic ring; R^3 , R^4 and R^5 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$,

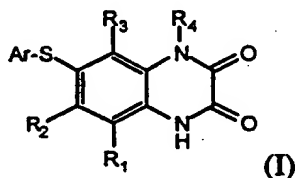
$-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{COR}^b$, $-\text{NR}^a\text{CO}_2\text{R}^b$, $-\text{COR}^a$, $-\text{CO}_2\text{R}^a$ or CONR^aR^b ; and R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group.

- 5 (41) 2-Phenylpyridazino[4,5-b]indole-1,4-dione derivatives (I) in GB 2 290 292 A as shown below:



- Compound of formula I, or a salt or prodrug thereof: wherein R^1 and R^2 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-\text{OR}^a$, $-\text{SR}^a$, $-\text{SOR}^a$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{COR}^b$, $-\text{NR}^a\text{CO}_2\text{R}^b$, $-\text{COR}^a$, $-\text{CO}_2\text{R}^a$ or $-\text{CONR}^a\text{R}^b$; or R^1 and R^2 together represent the residue of a carbocyclic or heterocyclic ring; R^3 , R^4 , R^5 and R^6 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-\text{OR}^a$, $-\text{SR}^a$, $-\text{SOR}^a$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{COR}^b$, $-\text{NR}^a\text{CO}_2\text{R}^b$, $-\text{COR}^a$, $-\text{CO}_2\text{R}^a$ or $-\text{CONR}^a\text{R}^b$; and R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group.

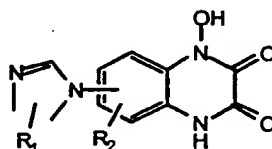
- (42) Arylthioxaline derivatives (I) in Tokkaihei 8-59660 as shown below:



Arylthioxaline derivatives of the formula (I) and its related salts, wherein R_1 is hydrogen, halogen, or nitro, R_2 is hydrogen, halogen, nitro, cyano, or trihalogenomethyl, R_3 is hydrogen, halogen, or nitro, R_4 is hydrogen, optionally

substituted lower alkyl, or optionally substituted lower cycloalkyl, and Ar is optionally substituted aromatic heterocyclic ring having at least one nitrogen atom.

(43) Hydroxyquinoxalinedione derivatives in Tokkaihei 7-165756 as shown below:

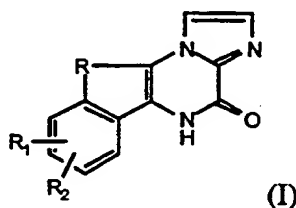


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The present invention relates to hydroxyquinoxalinedione derivatives of the above formula and its related salt, wherein R1 is hydrogen or lower alkyl, and R2 is nitro or trifluoromethyl.

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(44) Imidazo[1,2-a]pyrazin-4-one (I) in WO 95-02601 as shown below:



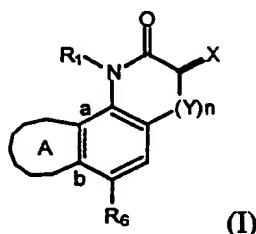
(I)

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Compounds of formula (I), wherein either R is C=R₃, C(R₄) R₅ or CH- R₆, R₁ and R₂ are hydrogen, halogen, alkyl, alkoxy, amino, acylamino, -NH-CO-NH-Ar, -N=CH-N(alk)alk', nitro, cyano, phenyl, imidazolyl or SO₃H, R₃ is oxygen, NOH, NO-alk-COOK or CH-R₇, R₄ is alkyl, -alk-Het or alk-Ar, R₅ is alkyl, -alk-Ar, or C(R₄) R₅ is cycloalkyl, R₆ is hydroxy, alkyl, NR₈ R₉, -alk-OH, -alk-NR₈ R₉, -alk-Ar or -alk-Het, R₇ is hydroxy, alkyl, phenyl, -alk-Ar, -alk-Het, NR₁₀ R₁₁ or a heterocyclic ring, R₈ and R₉ are alkyl, or R₈ is hydrogen and R₉ is hydrogen or alkyl, -COR₁₂, -CSR₃₀ or -SO₂ R₁₃, R₁₀ and R₁₁ are alkyl or cycloalkyl, R₁₂ is alkyl, cycloalkyl, phenyl, -COO-alk, -CH₂-COOX, -CH₂-NH₂, -NH-alk, -NH-Ar, -NH₂ or -NH-Het, R₁₃ is alkyl or phenyl, R₃₀ is -NH-alk, -NH-Ar, -NH₂ or -NH-Het; or R is a 2-imidazolylmethyl radical and each of R₁ and R₂ is a hydrogen atom.

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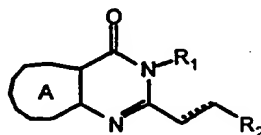
(45) AMPA antagonists (I) in WO 94-26747 as shown below:



Compounds having formula (I) or a pharmaceutically acceptable salt thereof wherein R^1 is hydrogen, alkyl, or benzyl; X is O or NOR^2 , wherein R^2 is hydrogen, alkyl or benzyl; Y is N-R^4 wherein R^4 is hydrogen, OH or alkyl; n is 0 or 1; R^6 is phenyl, naphthyl, thienyl, pyridyl, all of which may be substituted one or more times with substituents selected from the group consisting of halogen; CF_3 , NO_2 , amino, alkyl, alkoxy and phenyl; A is a ring of five to seven atoms fused with the benzo ring at the positions marked a and b.

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(46) 2,3-Disubstituted-(5,6)-heteroaryl fused-pyrimidine-4-ones in EP 0807 633 A2 as shown below:



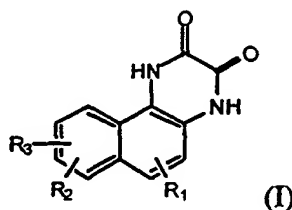
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2,3-Disubstituted-(5,6)-heteroaryl fused-pyrimidine-4-ones of formula (I) and their salts are new: ring A = a group of formula (i) or (ii) both optionally substituted by H, 1-6C alkyl, halo, CF_3 , $(\text{CH}_2)_n\text{NH}_2$, (1-6C alkyl)amino $(\text{CH}_2)_p$, di(1-6C alkyl)amino $(\text{CH}_2)_n$, 1-6C alkoxy, 1-6C hydroxyalkyl, (1-6C alkyl)O(1-6C alkyl), CN, (1-6C alkyl)COO(1-6C alkyl), (1-6C alkyl)OCOO(1-6C alkyl), (1-6C alkyl)COO, OH, NO_2 , R^3CO , R^4OCO , di(1-6C alkyl)NCO, 1-6C cycloalkyl, R^4NHCO or phenyl (optionally substituted); A, B, D, E = C or N; F, G, J = C, N, O or S with proviso; R^1 = Ph1 or pyridin-2-yl, pyridin-3-yl or pyridin-4-yl optionally substituted; Ph1 = a group of formula (iii); R^2 = Ph2 or a group of formula (iv) or (v); K, L, M = C or N provided

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that only one is N; P, Q, T = C, N, O or S provided that only one can be O or S and that at least one is a heteroatom; Ph₂ = a group of formula (vi); R³, R⁴ = H or 1-6C alkyl; R⁵ = H, 1-6C alkyl, halo, CF₃, 1-6C alkoxy or 1-6C alkylthio; R⁶-R⁸ = H or halo; R⁹ = e.g. H, 1-6C alkyl (optionally substituted), halo, CF₃, 1-6C alkoxy (optionally substituted), 1-6C alkylthio, (CH₂)_pOR¹³, (CH₂)_pNH(1-6C alkyl), (CH₂)_nN(1-6C alkyl)₂, (CH₂)_pNH(1-5C cycloalkyl) (sic), (CH₂)_pCONH₂, (CH₂)_n-CONH(1-6C alkyl), (CH₂)_pCON(1-6C alkyl)₂, (CH₂)_pCONH(1-5C cycloalkyl) (sic), (CH₂)_pCOOR¹³, (1-6C alkyl)OCO(1-6C alkyl), (1-6C alkyl)OCOO(1-6C alkyl), OCO(1-6C alkyl), (CH₂)_pNHCO(1-6C alkyl) or CN; R¹⁰, R¹⁴ = e.g. H, 1-6C alkyl (optionally substituted), halo, CF₃, 1-6C alkoxy (optionally substituted), 1-6C alkylthio, (CH₂)_pOR¹³, (CH₂)_nNH(1-6C alkyl), (CH₂)_pN(1-6C alkyl)₂, (CH₂)_pNH(1-5C cycloalkyl) (sic), COO(CH₂)_pR⁴, (CH₂)_pNH₂, 1-6C hydroxyalkyl, (1-6C alkyl)O(1-6C alkyl), CHO or CN; R¹¹, R¹² = H or halo; R¹³ = H, 1-6C alkyl, CO(1-6C alkyl), COO(1-6C alkyl), CONH(1-6C alkyl) or CON(1-6C alkyl)₂; R¹⁵-R¹⁷ = H, CN, 1-6C alkyl, halo, CF₃, CHO or 1-6C alkoxy; n, p = 0-3; provided that when R⁹ = H then one of R¹¹ and R¹² is not H.

(47) Quinoxaline compounds (I) in EP 0 511 152 A2 as shown below:

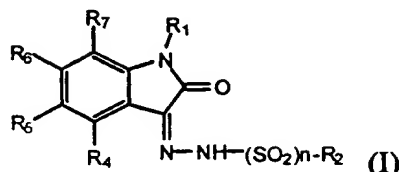


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Quinoxaline compounds having the formula I wherein R¹ is H, NO₂, CN, CF₃ or halogen, R² and R³ independently are H, CN, CF₃, halogen, C(NO₂) C₁₋₆ -alkyl, COR⁴ or SO₂R⁴ wherein R⁴ is C₁₋₆ -alkyl-, optionally substituted, or NR⁵R⁶ wherein R⁵, R⁶ independently are H, C₃₋₆ -cycloalkyl, is C₁₋₆-, optionally substituted, compositions thereof and methods of preparing the compounds are described.

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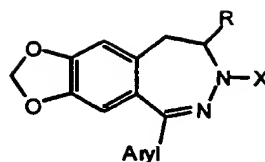
(48) Hydrazone derivatives in EP 0 503 349 A1 as shown below:



Hydrazone derivatives having the formula (I) wherein n is 0 or 1; R¹ is hydrogen, C₁₋₆-alkyl which may be branched, C₃₋₇-cycloalkyl, benzyl, phenyl which may be substituted, acyl, hydroxy, C₁₋₆-alkoxy, CH₂CO₂ R' is hydrogen or C₁₋₆-alkyl which may be branched, CH₂CN, CH₂CONR^{IV} R^V wherein R^{IV} and R^V independently are hydrogen or C₁₋₆-alkyl, or CH₂C(=NOH)-NH₂; R² is pyridyl or phenyl, both of which may be substituted one or more times preferably into the ortho and para positions with halogen, CF₃, NO₂, CN, phenyl, SO₂NR''R''' wherein R'' and R''' independently are hydrogen, benzyl, or C₁₋₆-alkyl; R⁴, R⁵, R⁶, R⁷ independently are hydrogen, C₁₋₆-alkyl which may be branched, phenyl, halogen, C₁₋₆-alkoxy, NO₂, CN, CF₃, or SO₂NR¹¹R¹² wherein R¹¹ and R¹² independently are hydrogen, benzyl, or C₁₋₆-alkyl; or R⁶ and R⁷ together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO₂, CF₃, CN, SO₂NR¹³R¹⁴ wherein R¹³ and R¹⁴ independently are hydrogen, benzyl, or C₁₋₆-alkyl; and R⁴ and R⁵ have the meanings set forth above; or R⁴ and R⁵ together form an additional 4 to 8 membered carbocyclic ring which may be aromatic or partial saturated and which may be substituted with halogen, NO₂, CF₃, CN, SO₂NR¹³R¹⁴ wherein R¹³ and R¹⁴ independently are hydrogen, benzyl, or C₁₋₆-alkyl; and R⁶ and R⁷ have the meanings set forth above.

(49) Dihydro-2,3-benzodiazepine derivatives (I) in EP 0 699 676 A1 as shown below:

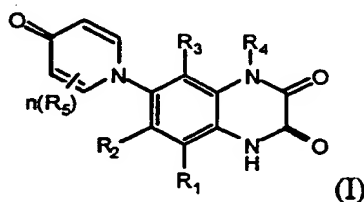
56



Dihydro-2,3-benzodiazepine derivatives represented by the formula I wherein R is methyl, X is acetyl and Aryl is p-nitrophenyl.

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(50) Oxopyridinylquinoxaline derivatives (I) in EP 0 676 397 A1 as shown below:

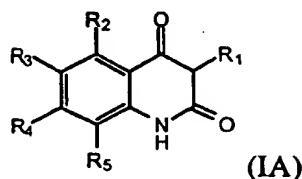


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An oxopyridinylquinoxaline derivative represented by the following formula I or pharmaceutically acceptable salts thereof wherein R¹ is hydrogen, halogen, nitro or trihalomethyl; R² is hydrogen, halogen, nitro, cyano, trihalomethyl, carbamoyl, carbomoyl substituted with lower alkyl, sulfamoyl, or sulfamoyl substituted with lower alkyl; R³ is hydrogen, nitro, or halogen; R⁴ is hydrogen, lower alkyl, substituted lower alkyl, lower cycloalkyl, or substituted lower cycloalkyl; R⁵'s are substituents independently selected from the group consisting of halogen, nitro, cyano, lower alkyl, carbamoyl, and carbamoyl substituted with lower alkyl; and n is an integer of 0 to 4.

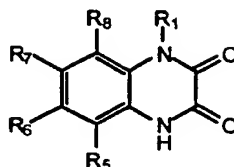
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(51) Dioxo-tetrahydroquinoline derivatives (IA) in EP 0 459 561 A2 as shown below:



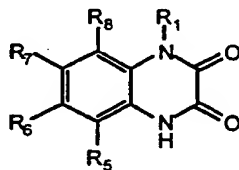
Dioxo-tetrahydroquinoline derivatives of formula (IA), wherein R^1 is a group of part formula (I) and (II); wherein U and V independently represent cyano, carboxy, -COR⁶, -CO₂ R⁶, -CO₂ SR⁶, -CONHOH or -CONHNH₂; n is zero or 1, preferably zero; T represents cyano, carboxy, -COR⁶, -CO₂ R⁶, -CONHOH or -CONHNH₂ or a group of formula in which the broken circle represents two non-adjacent double bonds in any position in the five-membered ring; B represents a bond or a carbonyl group (C=O); W, X, Y and Z represent oxygen, sulphur, nitrogen or carbon, provided that no more than one of W, X, Y and Z represents oxygen or sulphur, at least one of W, X, Y and Z represents carbon and at least one of W, X, Y and Z is other than carbon; one of E, F and G represents nitrogen or carbon and the remainder represent carbon; A¹, A² and A³ represent one, two or three substituents not exceeding the maximum number permissible by the disposition of heteroatoms in the five- or six-membered ring, which substituents are independently selected from hydrogen, hydrocarbon, halogen, cyano, trifluoromethyl, nitro, -OR^a, -SR^a, -SOR^a, -SO₂ R^a, SO₂ NR^aR^b, -NR^aR^b, -NR^a COR^b, -NR^aCO₂R^b, COR^a, -CO₂ R^a or -CONR^aR^b; or A¹ and A² or A² and A³ together represent the residue of an aromatic or heteroaromatic ring; R², R³, R⁴ and R⁵ independently represent hydrogen, hydrocarbon, halogen, cyano, trifluoromethyl, nitro, -OR^a, -SR^a, -SOR^a, -SO₂R^a, SO₂NR^aR^b, -NR^aR^b, -NR^a COR^b, -NR^aCO₂R^b, COR^a, -CO₂ R^a or -CONR^aR^b; or R² and R³, R³ and R⁴ or R⁴ and R⁵ together represent the residue of an aromatic or heteroaromatic ring; R⁶ represents hydrocarbon; and R^a and R^b independently represent hydrogen or hydrocarbon.

(52) Quinoxaline derivatives in EP 0 377 112 A1 as shown below:



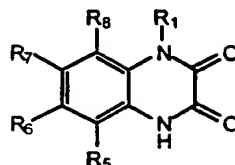
Heterocyclic dihydroxyquinoxaline compounds having the formula wherein R^1 is hydroxy, alkoxy, aryloxy, aralkyloxy, cycloalkylalkoxy, cycloalkoxy, or acyloxy; and R^5 , R^6 , R^7 and R^8 independently are hydrogen, NO_2 , halogen, CN, $\text{SO}_2 \text{NR}'\text{R}'$, $\text{SO}_2 \text{R}'$, CF_3 , or OR' , wherein R' is hydrogen or C_{1-4} -alkyl.

(53) Quinoxaline derivatives in EP 0 374 534 A1 as shown below:



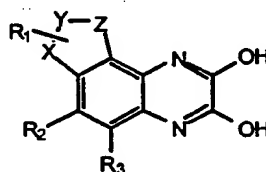
Heterocyclic dihydroxyquinoxaline compounds having the formula wherein R^1 is hydroxy, alkoxy, aryloxy, aralkyloxy, cycloalkylalkoxy, cycloalkoxy, or acyloxy; R^5 and R^6 together form a further fused ring, which may be substituted with hydrogen, halogen, or CN, and R^7 and R^8 independently are hydrogen, NO_2 , halogen, CN, $\text{SO}_2 \text{NR}'\text{R}'$, $\text{SO}_2 \text{R}'$, CF_3 , or OR' , wherein R' is hydrogen or C_{1-4} -alkyl; or R^7 and R^8 together form a further fused ring, which is substituted with hydrogen, halogen, or CN, and R^5 and R^6 independently are hydrogen, NO_2 , halogen, CN, $\text{SO}_2 \text{NR}'\text{R}'$, $\text{SO}_2 \text{R}'$, CF_3 , or OR' , wherein R' is hydrogen or C_{1-4} -alkyl.

(54) Quinoxaline derivatives in EP 0 315 959 A2 as shown below:



- Heterocyclic dihydroxyquinoxaline compounds having the formula wherein R^1 is C_{1-12} -alkyl, which may optionally be substituted by hydroxy, formyl, carboxy, carboxylic esters, amides or amines, C_{3-8} cycloalkyl, aryl, aralkyl; and wherein R^6 is hydrogen, halogen, CN, CF_3 , NO_2 , or OR' , wherein R' is C_{1-4} -alkyl and R^5 , R^7 and R^8 is hydrogen, provided R^6 is not CF_3 , OCH_3 , NO_2 , CL or Br when R^1 is CH_3 ; or R^6 and R^7 independently are NO_2 , halogen, CN, CF_3 , or OR' , wherein R' is C_{1-4} -alkyl and R^5 and R^8 are each hydrogen; or R^5 and R^6 together form a further fused aromatic ring, which may be substituted with halogen, NO_2 , CN, CF_3 or OR' , wherein R' is C_{1-4} -alkyl, and R^7 and R^8 independently are hydrogen, halogen, CN, CF_3 , NO_2 or OR' , wherein R' is C_{1-4} -alkyl; or R^7 and R^8 together form a further fused aromatic ring, which may be substituted with halogen, NO_2 , CN, CF_3 or OR' , wherein R' is C_{1-4} -alkyl, and R^5 and R^6 independently are hydrogen, halogen, CN, CF_3 , NO_2 or OR' , wherein R' is C_{1-4} -alkyl.

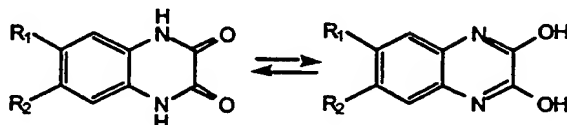
(55) Heterocyclic compounds in EP 0348 872 A1 as shown below:



Heterocyclic dihydroxyquinoxaline compounds having the formula wherein R^1 and R^2 independently are hydrogen, NO_2 , NH_2 , CN, halogen, SO_2NH_2 ; -X-Y-Z- is selected from $-N=N-NR^3-$, $-NR^3-N=N-$, $=N-NR^3-N=$, $-S-CH=N-$, $-N=CH-S-$, $-CH=C(CO_2 R^3)-S-$, $-S-C(CO_2 R^3)=CH-$, $=N-Se-N=$, $-N-CR^3-NR^3-$, $-NR^3-CR^3=N-$, $=N-O-N=$,

-N=CR³-CR³=N-, -NH-CR³=CR³-CR³=N-, -N=CR³-CR³=CR³-NH, =N-S-N=; wherein R³ is hydrogen, lower alkyl, CF₃.

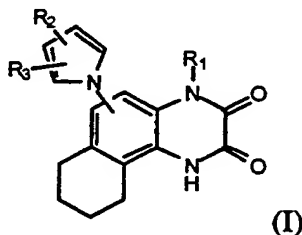
- 5 (56) Heterocyclic dihydroxyquinoxaline derivatives in US 4,812,458 as shown below:



Heterocyclic dihydroxyquinoxaline compounds having the formula wherein R¹ is halogen, CN, CF₃, ethynyl, or N₃ and R² is SO₂C₁₋₃-alkyl, CF₃, NO₂, ethynyl, or CN.

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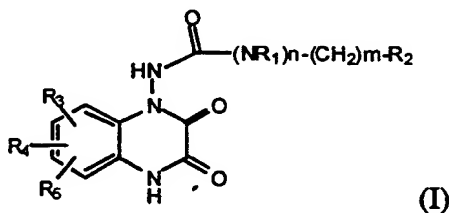
- (57) Pyrrolyl tetrahydrobenzoquinoxalinedione (I) in WO 96-11922 as shown below:



- 15 Pyrrolyl tetrahydrobenzoquinoxalinedione of formula I and their tautomeric and isomeric forms, as well as the pharmaceutically acceptable salts thereof, wherein R¹ hydrogen; an aliphatic residue with 1 to 6 C-atoms, which can carry one or two different substituents of the formula -COOR⁴, -CONHR⁴, -CO-R⁴, -OR⁴, -NHR⁴, -NH-CO-R⁴, -CONH-SO₂R⁴ or NHSO₂R⁴, of which R⁴ means hydrogen, C₁-C₄-alkyl, phenyl, benzyl, 1-phenylethyl or 2-phenylethyl, whereby the phenyl rings in R⁴ can be substituted by 1, 2 or 3 of the following substituents: C₁-C₄-alkyl, CF₃, C₁-C₄-alkoxy, F₃CO, halogen, nitro, CN, -OH, -CONHR⁵ and/or -COOR⁵ (R⁵ hydrogen, C₁-C₄-alkyl, phenyl or benzyl); -O-R⁶, of which R⁶ is hydrogen or an aliphatic residue with up to 4 C-atoms which can carry one of the following residues: -COOR⁴, -CONHR⁴, -NHCOR⁴, -NHSO₂R⁴, -OH or phenyl; R² hydrogen, C₁-C₄-alkyl or phenyl; R³ hydrogen or the residue -(CH₂)_m-R⁷, whereby m is the number 0, 1, 2, 3 or 4 and R⁷
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hydrogen, C₁-C₄-alkyl, phenyl, phenylsulfonyl, NO₂, CN, -COO-(CH₂)_n-R⁸, -CONH-(CH₂)_n-R⁸, -CONHSO₂R⁴, -CO-R⁸, -CH=CH-CONHR⁸, -CH=CH-COOR⁸, -CH=NOR⁸, -CH₂-NR⁸R⁹, CH₂NH-CY-(CH₂)_nR⁹, CH₂NH-CY-X-(CH₂)_n-R⁹, CH₂NH-CO-CF₃, CH₂NH-SO₂-R⁹ whereby X and Y independently of each other are oxygen or NH, n is the number 0, 1, 2, 3 or 4, R⁸ means hydrogen or linear or branched C₁-C₄-alkyl, which can be substituted by one or two phenyl- or pyridyl-residues, and R⁹ means hydrogen, linear or branched C₁-C₆-alkyl, phenyl or pyridyl, whereby all phenyl or pyridyl residues contained in R⁸ and R⁹ can carry one or two of the following residues: O-C₁-C₄-alkyl, F, Cl, Br, I, C₁-C₄-alkyl, NO₂, CF₃, -COOR⁵, -CONHR⁵, NH₂, CN, -SO₂phenyl, -NHSO₂R⁵, -NHCOR⁵, OH, -SO₂-C₁-C₄-alkyl, -NHCOCF₃, -SO₂R⁵ and -OCF₃.

(58) Amido-quinoxalinedione (I) in WO 95-35289 as shown below:



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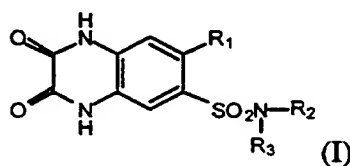
(I)

Amido-quinoxalinedione derivatives of formula (I), their tautomers, isomers and enantiomers, and their salts in which R¹ = H or 1-4C alkyl; n = 0-1; m = 0-4; R² = H, 1-6C alkyl or phenyl (optionally mono- or di-substituted with 1-4C alkyl, OR⁶, NH₂, NO₂, NHCOR⁶, CN, CF₃, OCF₃, CO₂R⁶, F, Cl, Br, I, COR⁶ or SO₂R⁶); R₃ = F, Cl, Br, I, 1-4C alkyl, OR⁷, COR⁷, NH₂, NO₂, NHCOR⁷, CF₃, CN; R₄, R₅ = H, 1-4C alkyl, 1-4C alkoxy, CF₃, OCF₃, F, Br, I, NO₂, CN or an annellated benzene ring (optionally mono or di-substituted with up to 2 1-4C alkyl, 1-4C alkoxy, CF₃, OCF₃, F, Br, I, NO₂, CN); R⁶ = H, 1-4C alkyl, phenyl or benzyl; R⁷ = H, 1-4C alkyl or CF₃; R⁸ = H, 1-4C alkyl, phenyl, phenylsulphonyl, NO₂, CN, COO(CH₂)_rR, CONH(CH₂)_rR, COR, CH=CHCONHR, CH₂NRR', CH₂NHCY(CH₂)_rR', CH=CHCOOR, CH=NOR,

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CH=NR, CH₂NHCY-Z(CH₂)_rR', CH₂NHCOCF₃ or a gp. of formula (b)-(f); R₉ = H or 1-4C alkyl; R = H, 1-4C alkyl, phenyl, benzyl, pyridyl or benzhydryl; R' = H, 1-4C alkyl, Ph, pyridyl or 4-(R-substituted)-piperidin-1-yl; Y = O or N; Z = O or NH; r = 0-4; q = 0-2; the benzene rings in R⁸, R and R' are optionally mono- or di-substituted with NH₂, OMe, OEt, Cl, Br, OCF₃, F, Me, Et, NO₂, COOR¹, CONHR¹, CH₂NHR¹, CH₂NHCOCF₃, CH₂NHCOMe, NHSO₂Me, NHCOMe or NHCOCF₃.

(59) Acid amide derivatives (I) in WO 95-31443 as shown below:



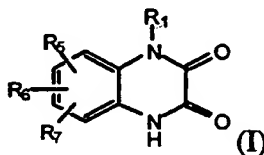
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Acid amides of the formula wherein R¹ represents hydrogen or nitro, R² and R³ stand, independently from each other, for hydrogen, lower alkyl or lower alkenyl optionally carrying a substituent selected from the group consisting of halogen, hydroxy, lower alkoxy, di(lower alkyl) amino, phenyl-lower alkoxy carbonyl and a 5- to 6-membered saturated hetero-ring containing 1 or 2 nitrogen and/or oxygen atom (s); or R² and R³ form, together with the adjacent nitrogen atom, a 6-membered saturated heterocyclic group containing optionally 1 or 2 additional nitrogen atoms and/or oxygen atoms (s), said ring optionally carrying a hydroxy or a hydroxy-lower alkyl group; and all of the possible mesomers, tautomeric forms and stereoisomers of the acid amides of the formula (I) and the mixtures thereof.

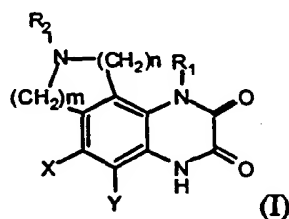
(60) Quinoxalindione derivatives (I) in WO 97-19066 as shown below:



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Quinoxalindione derivatives of formula (I), their isomers and salts are new: $R^1 =$
 $-(CH_2)_n-CR_2H-(CH_2)_m-Z$; $R^5 = 1-6C$ alkyl or $2-6C$ alkenyl (both optionally substituted
 by Q), SO_pR^{13} or $-CH=R^{15}$; Q = halo, OR^8 , NR^9R^{10} , SO_6R^{11} or COR^{12} ; or aryl or
 heteroaryl (both optionally substituted); R^6 , $R^7 = H$, halo, NO_2 , CN, $NR^{16}R^{17}$, COR^{14}
 5 or OR^{18} ; or aryl or heteroaryl (both optionally substituted); $1-6C$ alkyl or $2-6C$ alkenyl
 (both optionally substituted by Q), SO_pR^{13} or $-CH=R^{15}$; $R^2 = H$ or $-(CH_2)_qR^3$; $R^3 = H$,
 OH, $1-6C$ alkoxy or $NR^{19}R^{20}$; n, m, q = 0-3; Z = POXY, OPOXY, SO_2R^{21} $COOR^{22}$,
 CN or tetrazolyl; R^8 , $R^{18} = H$ or $1-6C$ alkyl (optionally halo substituted); o, p = 0-2;
 10 R^{11} , $R^{13} = H$, $1-6C$ alkyl or optionally substituted aryl; R^{12} , R^{14} , $R^{21} = OH$, $1-6C$
 alkoxy or $NR^{23}R^{24}$; $R^{15} = O$, $=NOH$ or a group of formula (a): X, Y = OH, $1-6C$
 alkoxy, $1-4C$ alkyl or $NR^{25}R^{26}$; R^9 and R^{10} , R^{16} and R^{17} , R^{19} and R^{20} , R^{23} and R^{24} , R^{25}
 and $R^{26} = H$, $1-4C$ alkyl, aryl, or together with the N atom form a 5-7 membered
 saturated heterocycle (optionally containing an additional O, S or N and optionally
 15 optionally substituted; provided that R^5 is not CF_3 or Me.

(61) N-substituted fused azacycloalkylquinoxalinediones (I) in WO 96-28445 as
 shown below:



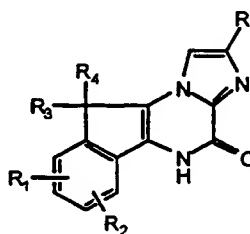
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In formula (I) m and n are independently 0,1 or 2 provided that m + n is > 1. R^1 is
 hydrogen, an alkyl or an alkylaryl; X and Y are independently hydrogen, halogen,
 nitro, cyano, trifluoromethyl, COOH, $CONR^4R^5$, SO_2CF_3 , SO_2R^4 , $SONR^4R^5$, alkyl,
 alkenyl, $(CH_2)_zCONR^4R^5$, $(CH_2)_zCOOR^4$, or $NHCOR^4$, wherein R^4 and R^5 are
 25 independently hydrogen, alkyl having 1 to 6 carbon atoms, cycloalkyl or alkylaryl, and
 z is an integer from 0 to 4; R^2 is alkyl $COOR^3$, alkylamine, alkylguanidine, aryl,

alkylaryl, COalkyl, COalkylaryl, CONR³alkyl, CONR³aryl, CONR³alkylaryl, CSNR³alkyl, CSNR³alkylaryl or a common amino acid moiety joined by an amide bond, wherein R³ is hydrogen, alkyl or alkylaryl.

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(62) Spiro[heterocycle-imidazo[1,2-a]indeno[1,2-e]pyrazine]-4'-ones (I) in WO 96-14318 as shown below:

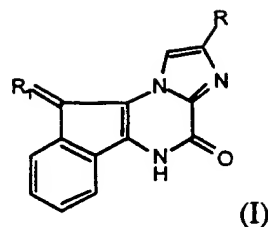


Compounds of formula (I), wherein R₃ and R₄, taken together with the carbon atom to which they are attached, form (a) a 2- or 3-pyrrolidine ring, a 2- or 4-piperidine ring or a 2-azacycloheptane ring, said rings being optionally substituted at the nitrogen atom by an alkyl radical, -CHO, -COOR₁₁, -CO-alk- COOR₆, -CO-alk-NR₆ R₁₂, -CO-alk-CONR₆R₈, -CO-COOR₆, -CO-CH₂-O-CH₂-COOR₆, -CO-CH₂-S-CH₂-COOR₆, -CO-alk, -CO-Ar¹¹, -CO-alk- Ar¹¹, -CO-NH-Ar¹¹, -CO-NH-alk-Ar¹¹, -CO-Het, -CO-alk-Het, -CO-NH-Het, -CO-NH-alk-Het, -CO-NH₂, -CO-NH-alk, -CO-N(alk)alk', -CS-NH₂, -CS-NH-alk, -CS-NH-Ar¹¹, -CS-NH-Het, -alk-Het, -alk- NR₆ R₈, -alk- Ar¹¹, -SO₂-alk, SO₂-Ar or -CO-cycloalkyl, where the cycloalkyl is optionally 2-substituted by a carboxy radical; or (b) a 2-pyrrolidine-5-one ring.

20

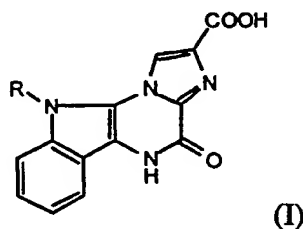
(63) 5H,10H-Imidazo[1,2-a]indeno[1,2-e]pyrazine-4-one derivatives (I) in WO 97-25327 as shown below:

65



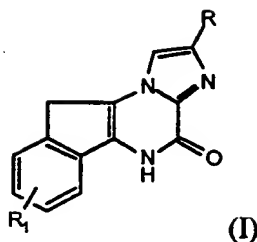
Compounds of formula (I), wherein R is a hydrogen atom or a -COOH or CH₂OH radical, R₁ is a -CH-R₂ radical, R₂ is a 3-dimethyl-1H-pyrazole-4-yl, 4-chloro-1-methylimidazole-5-yl or 3-hydroxy-isoxazole-5-yl radical except for 10-(1,3-dimethyl-1H-pyrazole-4-methylene)-5H, 10H-imidazo [1,2-a] indeno [1,2-e] pyrazine-4-one, isomers thereof, salts thereof, the preparation thereof and drugs containing said compounds.

(64) 5H,10H-Imidazo[1,2-a]indolo[3,2-e]pyrazine-4-one derivatives (I) in WO 97-25329 as shown below:



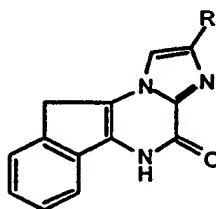
Compounds of formula (I) wherein R is a hydrogen atom or an -alk-COOH radical, racemic mixtures, enantiomers and diastereoisomers thereof, salts thereof, the preparation thereof and drugs containing said compounds.

(65) 5H,10H-Imidazo[1,2-a]indeno[1,2-e]pyrazine-4-one derivatives (I) in WO 97-25328 as shown below:



Compounds of formula (I), wherein R is a hydrogen atom or a -COOH, -alk-COOH, -PO₃H₂, CH₂-PO₃-H₂ or -CH=CH-COOH radical, or a phenyl radical substituted by a carboxy radical, R₁ is an alk-CN, -alk-COOH, alk-Het, alk-PO₃H₂ or -alk-CO-NH-SO₂R₂ radical, R₂ is an alkyl or phenyl radical, alk is an alkyl radical, Het is a saturated or unsaturated mono- or polycyclic heterocyclic ring containing 1-9 carbon atoms and one or more heteroatoms selected from O, S and N, said heterocyclic ring optionally being substituted by one or more alkyl, phenyl or phenylalkyl radicals, with the proviso that when R is a hydrogen atom or a -COOH or -PO₃H₂ radical, R₁ cannot be -alk-COOH, isomers, racemic, mixtures, enantiomers and diastereoisomers thereof, salts thereof, the preparation thereof, intermediates thereof and drugs containing said compounds.

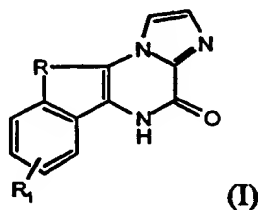
(66) 2-Substituted 5H,10H-imidazo[1,2-a]indeno[1,2-e]pyrazine-4-ones (I) in WO 97-25326 as shown below:



Compounds of formula (I), wherein R is a -CO-CH₂-PO₃H₂, -CO-NH-tetrazole-5-yl, -CO-NHOH, CO-NH-NH₂, -alk-COOH, -alk-COOalk', -CH₂-PO₃H₂, -CO-NH-SO₂-R₁ or -CH=CH-COOH radical, or a phenyl radical substituted by a carboxy radical, alk and alk' are an alkyl radical and R₁ is an alkyl, trifluoromethyl or phenyl radical optionally substituted by a carboxy or alkoxy-carbonyl radical, racemic mixtures,

isomers, enantiomers and diastereoisomers thereof, salts thereof, the preparation thereof and drugs containing said compounds.

5 (67) Indeno[1,2-e]pyrazine-4-ones (I) in WO 97-10246 as shown below:

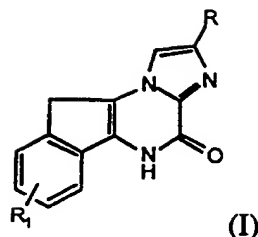


10 Compounds of formula (I), wherein R is a C=CH- R₂, C(R₃) R₄, CH- NH₂, CH-CH(OH)-COOH or CH-CH(OH)-COOalk radical, R₁ is an alk-NH₂ or alk-NH-CO-R₅ radical, R₂ is a -COOH or -COOalk radical, R₃ is an alkyl, -alk-Ar or -alk-Het radical, R₄ is an NH₂, -NH-alk, -N(alk)-alk', -NH-CO-alk, -NH-CO-Ar', -NH-CO-ALK-Ar', -NH-CO-Het, -NH-CO-alk-Het, -NH-CO-alk-COOH, -NH-CO-alk-COOalk', -alk-COOH, -alk-COOalk', -NH-CO-NH₂, -NH-CO-NH-alk or -NH-CO-NH-Ar' or -NH-CO-NH-alk-Ar' radical, or R₃ and R₄, together with the carbon atom to which they are attached, form a 2- or 3-pyrrolidine, 2- or 4-piperidine or 2-azacycloheptane substituted or unsubstituted ring, R₅ is an -NH₂, -NH-alk, -NH-Ar', -NH-cycloalkyl, -NH-alk-Ar' or -N(alk)-alk' radical, the salts thereof, the preparation thereof and medicaments containing same.

20

(68) 5H,10H-Imidazo[1,2-a]indeno[1,2-e]pyrazine-4-one derivatives (I) in WO 96-31511 as shown below:

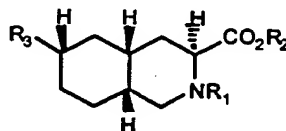
68



Compounds of formula (I), wherein R is a hydrogen atom or a carboxy, alkoxycarbonyl, $-\text{CO}-\text{NR}_4$, $-\text{PO}_3\text{H}_2$ or $-\text{CH}_2\text{OH}$ radical and R_1 is an $\text{alk}-\text{NH}_2$, $\text{alk}-\text{NH}-\text{CO}-\text{R}_3$, $\text{alk}-\text{COOR}_4$, $\text{alk}-\text{CO}-\text{NR}_5$, R_6 or $-\text{CO}-\text{NH}-\text{R}_7$ radical.

5

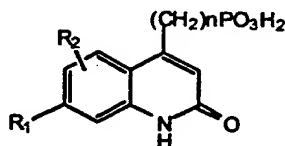
(69) Decahydroisoquinoline compounds (I) in US 5,356,902 as shown below:



10 Compound of the formula (I) wherein: R^1 is hydrogen, C_{1-10} alkyl, arylalkyl, alkoxycarbonyl, aryloxycarbonyl or acyl; R^2 is hydrogen, $\text{C}_1 - \text{C}_6$ alkyl, substituted alkyl cycloalkyl, or arylalkyl; R^3 is a group of the formula; R^4 is hydrogen, C_{1-4} alkyl, CF_3 , phenyl, bromo, iodo, or chloro; or a pharmaceutically acceptable salt thereof.

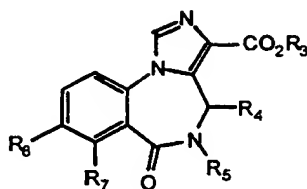
15

(70) Phosphonoalkylquinolin-2-ones in US 5,342,946 as shown below:



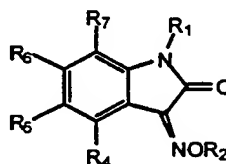
20 Having the general formula :wherein n is 0, 1, 2 or 3; R_1 and R_2 are selected from the group consisting of hydrogen, halogen, halomethyl, nitro, amino, alkoxy, hydroxyl, hydroxymethyl, C_1 to C_6 lower alkyl and C_7 to C_{12} higher alkyl, aryl, and aralkyl; and the pharmaceutically acceptable salts thereof.

(71) Imidazobenzodiazepine compounds (I) in US 5,270,306 as shown below:



Compound having the formula : wherein R^3 is hydrogen, C_{1-8} -alkyl which may be
 5 branched, or cycloalkylmethyl; R^7 and R^8 are independently hydrogen, halogen, CF_3 ,
 CN, NO_2 , NH_2 , C_{1-4} -alkyl or C_{1-4} -alkoxy; and R^4 is hydrogen and R^5 is hydrogen or
 C_{1-7} alkyl; or R^4 and R^5 together signify $(CH_2)_n$ wherein n is an integer of 2-3.

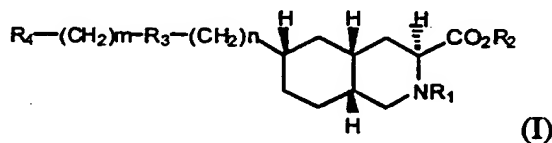
10 (72) Isatine derivatives in US 5,192,792 as shown below:



Indole-2,3-dione-3-oxime compound having the formula wherein R^1 is hydrogen, C_{1-6}
 15 -alkyl which may be branched, C_{3-7} -cyclo-alkyl, benzyl, phenyl which may be
 substituted, acyl, hydroxy, C_{1-6} -alkoxy, $CH_2 CO_2 R'$ wherein R' is hydrogen or C_{1-6} -
 alkyl which may be branched, CH_2CN , $CH_2CONR^{IV} R^V$ wherein R^{IV} and R^V
 independently are hydrogen or C_{1-6} -alkyl, or $CH_2C(=NOH)NH_2$; R^2 is (1) alkenyl of
 from two to six carbon atoms, preferably allyl, (2) alkynyl of from two to six carbons,
 20 preferably propargyl, (3) $(CH_2)_{1-6} CO_2 H$, (4) $(CH_2)_{1-6} CONHR$ wherein R is C_{1-6}
 alkyl, optionally branched; aryl which is phenyl optionally substituted by one or more
 of lower alkyl of from one to four carbons, halogen wherein halogen is fluoro, chloro,
 bromo, or iodo, trifluoromethyl, cyano, carboxy, alkoxycarbonyl wherein the alkoxy is
 of from one to four carbons, alkylthio wherein the alkyl is of from one to four carbons,

nitro, acyl of from two to four carbons, hydroxy, C₁₋₆ -alkoxy, CH₂ CO₂ R' wherein R' is hydrogen or C₁₋₆ -alkyl which may be branched, CH₂CN, CH₂CONR^{IV} R^V wherein R^{IV} and R^V independently are hydrogen or C₁₋₆ alkyl, optionally branched; aralkyl which is aryl as defined above attached through C₁₋₄ alkyl, or SO₂ R¹⁰ wherein R¹⁰ is C₁₋₆ alkyl, optionally branched; aryl which is phenyl optionally substituted by one or more of lower alkyl of from one to four carbons, halogen wherein halogen is fluoro, chloro, bromo, or iodo, tri-fluoromethyl, cyano, carboxy, alkoxycarbonyl wherein the alkoxy is of from one to four carbons, alkylthio wherein the alkyl is of from one to four carbons nitro, acyl of from two to four carbons, hydroxy, C₁₋₆ alkoxy, CH₂ CO₂ R' wherein R' is hydrogen or C₁₋₆ -alkyl which may be branched, CH₂CN, CH₂CONR^{IV} R^V wherein R^{IV} and R^V independently are hydrogen or C₁₋₆ alkyl, optionally branched; aralkyl which is aryl as defined above attached through C₁₋₄ alkyl; R₄, R₅, R₆, R₇ independently are hydrogen, C₁₋₆ alkyl, which may be branched, phenyl, halogen, C₁₋₆ -alkoxy, NO₂, CN, CF₃, or SO₂NR''R''' wherein R'' and R''' independently are hydrogen, or C₁₋₆ -alkyl; or R⁶ and R⁷ together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen, NO₂, CF₃, CN, SR₂NR''R''' wherein R'' and R''' independently are hydrogen, or C₁₋₆ -alkyl; and R⁴ and R⁵ have the meanings set forth above.

(73) Aryl-spaced decahydroisoquinoline-3-carboxylic acids in US 5,446,051:

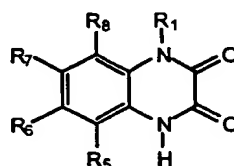


Preferably, the compounds are of the general formula (I) wherein R¹ is H, C₁-C₁₀ -alkyl, arylalkyl, alkoxycarbonyl, aryloxycarbonyl, or acyl; R₂ is H, C₁ -C₆-alkyl, substituted alkyl, C₄- C₇ cycloalkyl or arylalkyl; R₃ is aryl, arylalkyl, heterocycle,

substituted heterocycle, C₄- C₇ cycloalkyl or C₄- C₇ cycloalkenyl; R₄ is CO₂H, SO₃H, PO₃H₂, or one of the following cyclic compounds : wherein R⁵ is H, C₁₋₆ -alkyl or aryl; m = 0, 1 or 2; and n = 0, 1 or 2; or a pharmaceutically acceptable salt thereof.

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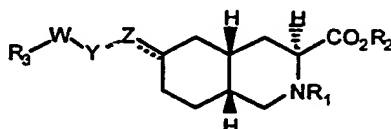
(74) Quinoxalindione derivatives reported in WO 94-25469 and shown below:



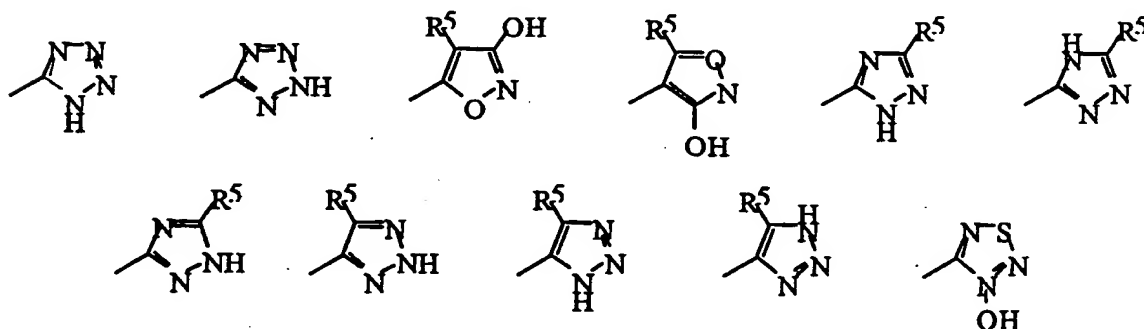
Quinoxalindione derivatives represented by the above formula wherein R₁ is (CH₂)_n-CR₂H-(CH₂)_m-Z and R₅, R₆, R₇ and R₈ together or independently are hydrogen, C₁-C₆ alkyl, CF₃, nitro, halogen, NR₉R₁₀, cyano, SO_pR₁₁, SO₂NR₁₂R₁₃, SO₃H, SO₃C₁₋₆-alkyl or OR₁₄; R₂ is hydrogen, or (CH₂)_q-R₃; R₃ is hydrogen, OH, C₁₋₆-alkoxy or NR₁₅R₁₆, and n, m and q are 0,1,2, or 3; Z is POXY, OPOXY, OR₁₇, NR₁₈R₁₉, NH-COR₂₀, NH-SO₂R₂₁, SO₂R₂₂, CO₂R₂₃, halogen, cyano or tetrazole; R₁₁ is hydrogen, C₁-C₆ alkyl, phenyl; p is 0, 1, or 2; R₁₂, R₁₃, R₁₇ or R₂₃ is hydrogen or C₁-C₄ alkyl; R₁₄ is hydrogen or 1-3 halogen substituted C₁-C₆ alkyl; R₂₀ and R₂₁ are C₁-C₆ alkyl or halogen substituted phenyl or hetaryl; R₂₂ is OH, C₁-C₆ alkoxy or NR₂₄R₂₅; X and Y are together or independently OH, C₁-C₆ alkoxy, C₁-C₄ alkyl or NR₁₈R₁₉; R₉ and R₁₀ are together or independently hydrogen, CO-C₁-C₆ alkyl, phenyl or C₁-C₆ alkyl, which may be substituted with C₁-C₄ alkoxy or C₁-C₄ alkyl mono- or disubstituted NH₂ group, or together with the nitrogen form a 5-7 membered heterocyclic ring which may contain additional N, S or O and can be substituted, or form five membered heterocyclic ring which may contain 1-3 nitrogens and can be substituted; R₁₅ and R₁₆, R₁₈ and R₁₉ together or independently are hydrogen, C₁-C₄ alkyl, phenyl or together with the oxygen form 5-7 membered heterocyclic ring which may contain additional N, S or O and can be substituted, or form five membered heterocyclic ring which may contain 1-3 nitrogens and can be substituted; R₂₄ and R₂₅ together or independently are hydrogen, C₁-C₄

alkyl, or together with the oxygen form 5-7 membered heterocyclic ring which may contain additional N, S or O, and their isomers and salts and provided R₂ is hydrogen and Z POXY or CO₂R₂₃ then R₅-R₈ is not hydrogen; and provided R₂ is hydrogen, Z POXY or CO₂R₂₃ and R₅, R₆, R₇ and R₈ are CF₃, NO₂, halogen, NH₂ or methyl, the compounds of the above formula are double-substituted and provided R₁ is methanophosphonic acid and R₆ cyano or substituted imidazole then together R₅, R₇ and R₈ is not hydrogen and provided R₁ is methanosulphonic acid and R₆ is CF₃ or NO₂ and R₇ is imidazole, R₅ and R₈ is not hydrogen; and provided R₁ is CH₂-COOH and R₅ and R₈ is hydrogen, R₆ and R₇ is not halogen or methyl; and the pharmaceutically acceptable salts thereof.

(75) Isoquinolinyl-carboxylic acid compounds reported in US 5,606,062 and shown below:

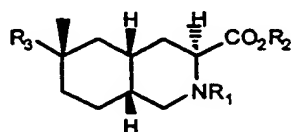


Isoquinolinyl-carboxylic acid compounds represented by the above formula wherein R₁ is hydrogen, C₁-C₁₀ alkyl, arylalkyl, alkoxycarbonyl, or acyl; R₂ is hydrogen, C₁-C₆ alkyl, substituted alkyl, cycloalkyl, or arylalkyl; R₃ is CO₂H, SO₃H, CONHSO₂R₈, or a group of formula:

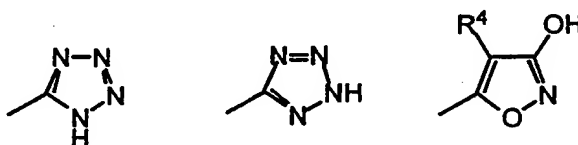


W is $(\text{CH}_2)_n$, S, SO, SO_2 ; Y is CHR7, NR_4 , O, S, SO, or SO_2 ; Z is NR_6 , CHR7, or CH; or W and Y together are $\text{HC}=\text{CH}$ or $\text{C}\equiv\text{C}$, or Y and Z together are $\text{HC}=\text{CH}$ or $\text{C}\equiv\text{C}$; R_4 is hydrogen, C1-C4 alkyl, phenyl, or acyl; R_5 is hydrogen, C1-C4 alkyl, CF_3 , phenyl, hydroxy, amino, bromo, iodo, or chloro; R_6 is acyl; R_7 is independently hydrogen, C1-C4 alkyl, phenyl, or substituted phenyl; R_8 is C1-C4 alkyl or tetrazole-5-yl; and n is 0, 1, or 2; provided that when Y is NR_4 , O, S, SO, or SO_2 , W is $(\text{CH}_2)_n$ and Z is CHR7 or CH; further provided that when W is S, SO, or SO_2 , Y is CHR7, Z is CHR7 or CH or Y and Z together are $\text{HC}=\text{CH}$ or $\text{C}\equiv\text{C}$; further provided that when W and Z are CH_2 , Y is not S; further provided that when W and Y together are $\text{HC}=\text{CH}$ or $\text{C}\equiv\text{C}$, Z is CHR7; and the pharmaceutically acceptable salts thereof.

(76) Decahydroisoquinoline compounds described in US 5,527,810 as shown below:

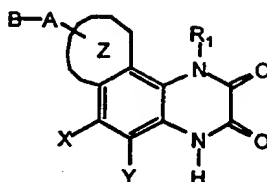


Decahydroisoquinoline represented by the above formula wherein R_1 is hydrogen, C1-C10 alkyl, arylalkyl, alkoxycarbonyl, aryloxycarbonyl or acyl; R_2 is hydrogen, C1-C6 alkyl, substituted alkyl, cycloalkyl, or arylalkyl; R_3 is a group of the formula:



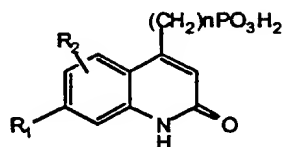
R_4 is hydrogen, C1-C4 alkyl, CF_3 , phenyl, bromo, iodo, or chloro, and the pharmaceutically acceptable salts thereof.

(77) Cycloalkynoxalinediones shown in US 5,721,234 as exemplified below:



Cycloalkynoxalinediones represented by the above formula wherein Z is an alicyclic fused ring having 5 to 7 carbon atoms; R1 is hydrogen, an alkyl or an arylalkyl; X and Y are independently hydrogen, halogen, nitro, cyano, COOH, CONR₂R₃, SONR₂R₃ wherein R₂ and R₃ are independently hydrogen, alkyl having 1 to 6 carbon atoms, cycloalkyl or aralkyl; and A is O, CH₂, NR₄, CH₂NR₄, CN, tetrazole or CO wherein R₄ is hydrogen, alkyl, hydroxyalkyl, aminoalkylamine or aralkyl, wherein (i) when A is O, CH₂, NR₄, or CH₂NR₄ then B is hydrogen, alkyl, alkenyl, aryl, aralkyl, hydroxyalkyl, alkoxy, aminoalkyl, heterocyclic, alkylheterocyclic, heterocyclic-methyl, heterocyclic-ethyl, alkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heterocyclic-carbonyl, alkylheterocyclic-carbonyl, any of which may be unsubstituted or substituted by one or more hydroxy, CO₂H, mercapto, amino, alkyl or butoxycarbonyl group, CONR₅R₆ wherein R₅ is hydrogen, alkyl having 1 to 6 carbon atoms, or aralkyl, and R₆ is alkyl, aryl, or aralkyl, or N, R₅, and R₆ taken together form a cyclic amine, or when A is NR₄ or CH₂NR₄ then B is a common amino acid moiety joined by an amide bond or B joins with R₄ and the nitrogen to form a four to seven membered heterocyclic ring, provided that when Z is a fused cyclohexyl ring and R₄ is hydrogen then B is not hydrogen; (ii) when A is CN then B is not present and Z is not a fused cyclohexyl ring; (iii) when A is tetrazole then B is hydrogen or alkyl having 1 to 6 carbon atoms; and (iv) when A is CO then B is hydroxy, alkoxy, aralkoxy, alkyl having 1 to 6 carbon atoms, aralkyl, NR₇R₈ wherein R₇ is hydrogen, alkyl having 1 to 6 carbon atoms, or aralkyl, and R₈ is alkyl, aryl, or aralkyl, or N, R₇, and R₈ taken together from a cyclic amine, and the pharmaceutically acceptable salts thereof.

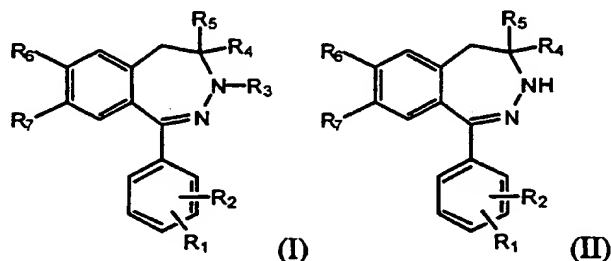
(78) Phosphonoalkylquinolin-2-ones as reported in US 5,510,338 and shown below:



Phosphonoalkylquinolin-2-ones represented by the above formula wherein n is 0, 1, 2
 5 or 3. R1 or R2 are selected from the group consisting of hydrogen, halogen, halomethyl, nitro, amino, alkoxy, hydroxyl, hydroxymethyl, C1 to C6 lower alkyl and C7 to C12 higher alkyl, aryl, and aralkyl; and the pharmaceutically acceptable salts thereof.

10

(79) 2,3-Benzodiazepine derivatives (I) and (II) in P 97 00688 as shown below:

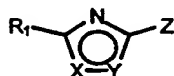


2,3-Benzodiazepine derivatives and medicinal preparations containing such drugs represented by the formula I wherein R1 and R2 can be, independently from each
 15 other, hydrogen, halogen, alkyl group with 1-4 carbonic atoms, alkoxy group with 1-4 carbonic atoms, nitro group, trifluoromethyl group, or group having a general structure of -NR8R9, where the meaning of R8 and R9, can be, independently from each other, hydrogen, alkyl group with 1-4 carbonic atoms, or group having a general structure of -COR10, where R10 means hydrogen atom, alkyl group with 1-6 carbonic atoms
 20 substituted in given cases, aryl group with 6-10 carbonic atoms, alkoxy group with 1-4 carbonic atoms, cycloalkyl group with 3-5 carbonic atoms, alkenyl group with 2-6 carbonic atoms, cycloalkoxy group with 3-5 carbonic atoms, or group having a general structure of -NR11R12, where the meaning of R11 and R12, independently from each

other, hydrogen atom, alkyl group with 1-4 carbonic atoms, cycloalkyl group with 3-5 carbonic atoms, or aryl group with 6-10 carbonic atoms, the meaning of R3 can be alkyl group with 1-4 carbonic atoms, cycloalkyl group with 3-5 carbonic atoms, or group having a general structure of -CO-R13, where the meaning of R13 can be the same as given for R10, the meaning of R4 and R5, can be, independently from each other, hydrogen atom, or alkyl group with 1-3 carbonic atoms, the meaning of R6 and R7, can be, independently from each other, hydrogen atom, Cl atom, or Br atom, with the condition that if any of R4 or R5 means hydrogen atom, the second can only be other than hydrogen atom, further, the isomers, salts obtained with acid addition, and the medicinal preparations originating from them.

2,3-Benzodiazepine derivatives represented by the formula II wherein R1, R2, R4, R5, R6 and R7 is given for general structure (I).

(80) Oxadiazole derivatives (I) in DE 196 43 037 A1 as shown below:

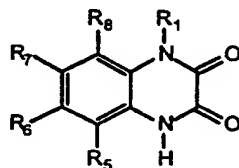


Oxadiazole derivatives of formula (I), and their racemates, enantiomers, diastereomers, mixtures and acid addition salts, are new. One of X, Y = N and the other = O; Z = pyridyl substituted by S1, or Ar (optionally substituted by R² and R³); Ar = phenyl substituted at the 2-position by S1 and optionally at the 6-position by S2; or Ar = phenyl substituted at the 3- or 4- position by S2; S1 = B-V-D-R⁴, B-N(D-R⁴)D-R⁴¹ or a group of formula (a) (optionally substituted by halo, oxo, OR7, OCOR7, 1-4C alkyl, 2-6C alkenyl or 2-6C alkynyl); S2 = B-V-D-R⁴ or B-N(D-R⁴)D-R⁴¹; V, E = O, S or NR⁷; D = 1-10C alkylene, 2-10C alkenylene or 2-10C alkynylene (all optionally substituted by Q1); B = bond or as for D; n, m = 1-3, and n+m is at least 2; R¹ = 1-10C alkyl, 2-10C alkenyl or 2-10C alkynyl (all optionally substituted by one or more Q2), a norbornane, norbornene, di(3-6C)cycloalkyl-methyl, adamantane or noradamantane residue (all optionally substituted by 1-4C alkyl), H, phenyl

(optionally substituted by 1-3 Q3 (directly or via 1-4C alkylene)), phenyl (substituted by B-N(D-R⁴)DR⁴¹, B-V-D-R⁴, OCH₂O or OCH₂CH₂O), A"-A', 3-7C cycloalkyl (optionally substituted by Q2), fluorenyl, a [3.3.0]bicyclooctane group; or an optionally substituted group of formula (b)-(d); y = 1 or 2; z = 0-2; R², R³ = 1-10C alkyl, 2-10C alkenyl or 2-10C alkynyl (all optionally substituted by Q2), SH, NR⁵R⁶, halo, NO₂, CF₃, OR⁷, SR⁷, COOR⁷, 6-10C aryl, aryl(1-6C)alkyl or 6-10C aryloxy; or R²+R³ complete an unsaturated fused 5-7 membered ring (optionally containing one or more heteroatoms, and optionally substituted by OR⁷, NR⁵R⁶, halo, CN, NO₂, CF₃, COOR⁷, 1-10C alkyl, 2-10C alkenyl or 2-10C alkynyl; R⁴, R⁴¹ = 1-10C alkoxy, 2-10C alkenyloxy or 2-10C alkynyloxy (all optionally substituted by Q2), OH, halo, NO₂, CF₃, CN, SH, 1-6C alkylmercapto, A-Ar', OAr', Ar'-substituted 1-6C alkoxy, M', NR⁵R⁶ or 3-8C cycloalkoxy (optionally substituted by oxo, OR⁷ or OCOR⁷); R⁵, R⁶ = 1-10C alkyl, 2-10C alkenyl or 2-10C alkynyl (all optionally substituted by OH, optionally substituted phenyl, optionally substituted benzyl, NR⁷R⁷¹ or 1-8C alkoxy), H, optionally substituted 3-6C cycloalkyl or 6-10C aryl (optionally substituted by halo, OR⁷, 1-4C alkyl, NR⁷R⁷¹, SO₃H or COOR⁷); or NR⁵R⁶ = an optionally unsaturated 5-6 membered ring, optionally containing other heteroatoms, and optionally substituted by Q4; R⁷, R⁷¹ = H, R, 2-4C alkenyl, 2-4C alkynyl, or benzyl or phenyl (both optionally substituted by OH, Cl, Br or OMe); R⁸ = 1-4C alkyl, 2-4C alkenyl, 2-4C alkynyl, phenyl, benzyl or 3-6C cycloalkyl; R⁹ = H, 1-4C alkyl, COOR⁷, CH₂OR⁷, CONR⁵R⁶ or phenyl; Q1 = CN, CHO, COOR⁷, CONHSO₂R⁷, CONR⁵R⁶, CH=NOR⁷, COR⁸, CH(OR⁷)R⁸, CH(OR⁷)OR⁷¹, CH=CHR⁹, NR⁵R⁶, NHCOR⁷, NHCONR⁵R⁶, NHCOOR⁷, OR⁷, OCOR⁷, OCOOR⁷, OCONR⁵R⁶, SR⁷, SOR⁷, SO₂R⁷, SO₃H, SO₂NR⁵R⁶, halo, 1,3-dioxolan or 1,3-dioxan); Q2 = oxo or Q1; A" = 1-6C-alkyl, 2-6C alkenyl or 2-6C alkynyl; A = H or as for A"; A' = phenyl (optionally ring substituted, directly or via a 1-4C alkylene bridge, by one or more groups Q3), 3-7C cycloalkyl (optionally ring substituted, directly or via a 1-4C alkylene bridge, by one or more groups Q2), M, CONHM or NHCOM; Ar' = aryl substituted by one or more Q3; M' = 5-7 membered heterocycle linked via C, containing one or more heteroatoms, optionally substituted by benzyl, 1-4C alkyl, halo, OR⁷, CN, NO₂, NH₂,

CH₂NR⁵R⁶, OH, oxo, ketal, ethylene ketal, COOH, SO₃H, COOR⁷, CONR⁵R⁶, COR⁸, SO₂R⁷ or CONR⁵R⁶ (sic)); M = heterocycle as for M', (which may also be linked by N, and also be substituted by optionally substituted phenyl or substituted benzyl); Q3 = halo, 1-4C alkyl, CF₃, CHO, COOR⁷, CONHSO₂R⁷, CONR⁵R⁶, CH=NOR⁷, COR⁸, CH(OH)R⁸, CH(OR⁷)OR⁷¹, CH=CHR⁹, NR⁵R⁶, NO₂, 1-4C alkyl-NR⁵R⁶, NHCOR⁷, NHCONR⁵R⁶, NHCOOR⁷, NH-SO₂R⁷, OR⁷, OCOR⁷, OCONR⁵R⁶, SR⁷, SOR⁷, SO₂R⁷, SO₃H or SO₂NR⁵R⁶; Q4 = 1-4C alkyl, (CH₂)_n-Q5, halo, OR⁷, CN, NO₂, NR⁷R⁷, SO₃H, COOR⁷, CONR⁷R⁷¹, SO₂R⁷, oxo or a ketal; Q5 = phenyl, NH₂, 1-4C alkylamino, di(1-8C)alkylamino or NHCOOR⁷; heteroatoms = N, O, S.

(81) Quinoxalindione derivatives reported in WO 96-37500 and shown below:



Quinoxalindione derivatives represented by the formula I wherein R¹ is -(CH₂)_nCR²H- (CH₂)_m-Z and R⁵, R⁶, R⁷ and R⁸ together or independently are hydrogen, C₁₋₆-alkyl in which one or more hydrogen atoms are replaced with halogen atoms, nitro, halogen, NR⁹R¹⁰, cyano, SO_pR¹¹, SO₂NR¹²R¹³, SO₃H, SO₃C₁₋₆-alkyl or OR¹⁴; R² hydrogen or (CH₂)_q-R³; R³ hydrogen, hydroxy, C₁₋₆-alkoxy or NR¹⁵R¹⁶; n, m and q can be 0, 1, 2 or 3; Z is POXY, OPOXY, SO₂R¹⁷, COR¹⁸, halogen, cyano or tetrazole; R¹¹ H, C₁₋₆-alkyl, phenyl; p 0, 1 or 2; R¹² and R¹³ are independently hydrogen or C₁₋₄-alkyl; R¹⁴ A-R¹⁹, or means C₆₋₁₂-aryl- or hetaryl, which can be substituted with halogen, C₁₋₆-alkoxy, hydroxy, cyano, NR²⁰R²¹, eventually with halogen substituted C₁₋₆-alkyl and/or COR²² and A linear or branched, saturated or unsaturated alkyls with C₁₋₂₀-carbon atoms in which one or several carbons can be substituted by O, S and/or NR²⁶ and can be substituted with halogen; and R¹⁹ hydrogen, NR²⁴R²⁵, halogen, C₁₋₆-alkyl, which eventually is substituted with halogen, C₁₋₆-alkoxy, COR²³, CN or one C₆₋₁₂-aryl

or hetaryl which is substituted with halogen, and/or substituted COR²²; and R¹⁸ hydrogen, C₁₋₄-alkyl, hydroxy, C₁₋₆-alkoxy or NR²⁷R²⁸; R¹⁷, R²² and R²³ hydroxy, C₁₋₆-alkoxy or NR²⁹R³⁰, R²⁶ hydrogen, C₁₋₆-alkyl, C₁₋₆-alkenyl, X and Y are similar or different and are hydroxy, C₁₋₆-alkoxy, C₁₋₄-alkyl or NR²⁷R²⁸; R⁹ and R¹⁰, R²⁰ and R²¹ and/or R²⁵ and R²⁴, are similar or different and hydrogen, CO-C₁₋₆-alkyl, phenyl or C₁₋₆-alkyl, which with C₁₋₄-alkoxy or one eventually with C₁₋₄-alkyl mono- or di-substituted aminogroup substituted is, or together with nitrogen atom bild 5-7-membered saturated heterocyclic ring, which may contain additional N, S- or O-atom and can be substituted, or bild 5-membered saturated heterocyclic ring, which contains 1-3 N atoms and can be substituted; R¹⁵ and R¹⁶, R²⁷ and R²⁸, R²⁹ and R³⁰ are similar or different and are hydrogen, C₁₋₄-alkyl, phenyl or bild together with nitrogen atom 5-7-membered saturated heterocyclic ring, which may contain additional O-, S-, N-atom and can be substituted or bild 5-membered saturated heterocyclic ring, which can contain 1-3 nitrogen atoms and can be substituted, although R⁵-R⁸ always mean OR¹⁴, and R¹⁴ does not mean H or eventuell 1-3 halogen substituted C₁₋₆-alkyl.

AMPA and/or kainate receptor channel blocker

The inhibitors of the present invention also include AMPA and/or kainate receptor channel blockers. The term "AMPA and/or kainate receptor channel blockers" is used to refer to moieties that reduce the permeability of channels associated with the AMPA and/or kainate receptor to cations (preferably to Na⁺, K⁺ and/or Ca²⁺ ions). AMPA and/or kainate receptor channel blockers can therefore be used to prevent a signal being transmitted due to ionic flux that would otherwise occur when glutamate binds to the AMPA and/or kainate receptor.

AMPA and/or kainate receptor channel inhibitors include e.g. fluorowillardiine and Joro spider toxin.

Having described the inhibitors of the present invention, their therapeutic uses will now be discussed in greater detail.

Therapeutic uses

5

Inhibitors of the present invention may be used in human and veterinary medicine. Treatments may be prophylactic or may be in respect of existing conditions.

10

As explained supra, the inhibitors may be used in the manufacture of a medicament for treating a demyelinating disorder. The term "demyelinating disorder" is used herein to include any disorder that results in a reduced level of myelination.

15

Demylinating disorders include acute disseminated encephalomyelitis, acute demyelinating polyneuropathy (Guillain Barre syndrome), chronic inflammatory demyelinating polyneuropathy, multiple sclerosis, Marchifava-Bignami disease, central pontine myelinolysis, Devic syndrome, Balo disease, HIV- and HTLV-myelopathy, and progressive multifocal leucoencephalopathy.

20

Demylinating disorders also include secondary demyelinating disorders - i.e. where bystander myelin loss occurs as a consequence of a secondary pathological insult.

Examples of secondary demyelinating disorders are CNS lupus erythematoses, polyarteriitis nodosa, Sjögren syndrome, sarcoidosis and isolated cerebral vasulitis.

25

The present invention includes within its scope pharmaceutically acceptable compositions useful in treating demyelinating disorders which comprise an inhibitor of the present invention. The inhibitor will usually be provided in combination with a pharmaceutically acceptable carrier. It may be used in any suitable form, provided that it can still act in inhibiting the interaction of glutamate with the AMPA and/or kainate receptor complex. For example, pharmaceutically acceptable salts, esters, hydrates, etc. may often be used.

30

Pharmaceutical compositions within the scope of the present invention may include one or more of the following: preserving agents, solubilising agents, stabilising agents, wetting agents, emulsifiers, sweeteners, colorants, odourants, salts, buffers, coating agents or antioxidants.

5

They may contain a further therapeutically active agent in addition to an inhibitor of the present invention. The further therapeutically active agent may be an immunosuppressive agent (e.g. corticotrophin, a glucocorticoid, cyclophosphamide, cyclosporine, azothioprine or mitozantrone), an interferon (IFN; IFN-beta-1a e.g. Rebif and Avonex; IFN-beta-1b e.g. Betaseron and Betaferon; IFN-alpha-2a e.g. Alphaferone; IFN-alpha-2b e.g. Viraferon), a phosphodiesterase type IV inhibitor, a humanised monoclonal antibody against a leukocyte adhesion molecule (e.g. Antegran), a synthetic polypeptide (e.g. glatiramer acetate, copolymer-1) a tissue matrix metalloproteinase (MMP) inhibitor (e.g. hydroxamic acid-based inhibitors of MMPs) or a tumour necrosis factor (TNF) inhibitor (e.g. Thalidomide or TNF-receptor immunoglobulin fusion protein).

The combination of an inhibitor of the present invention and a further therapeutically active agent may be used simultaneously, separately or sequentially to treat a demyelinating disorder. It may provide synergistically effective combination. The further therapeutically active agent may be an immunosuppressive agent (e.g. corticotrophin, a glucocorticoid, cyclophosphamide, cyclosporine, azothioprine or mitozantrone), an interferon (IFN; IFN-beta-1a e.g. Rebif and Avonex; IFN-beta-1b e.g. Betaseron and Betaferon; IFN-alpha-2a e.g. Alphaferone; IFN-alpha-2b e.g. Viraferon), a phosphodiesterase type IV inhibitor, a humanised monoclonal antibody against a leukocyte adhesion molecule (e.g. Antegran), a synthetic polypeptide (e.g. glatiramer acetate, copolymer-1) a tissue matrix metalloproteinase (MMP) inhibitor (e.g. hydroxamic acid-based inhibitors of MMPs) or a tumour necrosis factor (TNF) inhibitor (e.g. Thalidomide or TNF-receptor immunoglobulin fusion protein).

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A pharmaceutical composition within the scope of the present invention may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) routes. Such a composition may be prepared by any method known in the art of pharmacy, for example by admixing one or more active ingredients with a suitable carrier. Preferably it will be provided in unit dosage form. It will normally be provided in a sealed, sterile container e.g. in an ampoule, a vial, a bottle, a blister pack, etc.

Different drug delivery systems can be used to administer pharmaceutical compositions of the present invention, depending upon the desired route of administration. Such systems include tablets, capsules, lozenges, pastilles, powders, solutions, suspensions, syrups, ointments, pastes, oils, aerosols, suppositories, enemas, pessaries, tampons, sprays, nebulizers, injectable compositions, etc.

Dosages of the inhibitors of the present invention can vary between wide limits, depending upon the nature of the treatment and the age and condition of the individual to be treated. However, a daily dosage of from 0.5 mg to 1000 mg, preferably of from 50-200 mg may be suitable. The dosage may be repeated as often as appropriate. If side-effects develop, the amount and/or frequency of the dosage can be reduced, in accordance with good clinical practice.

The therapeutic uses of the present invention are based upon animal models that are discussed in the examples and that are believed to be reliable. Prior to the present invention there was no disclosure of the use of antagonists of the present invention for treating demyelinating disorders. Only limited characterisation studies of kainate and AMPA receptors had been performed. Matute *et al* had performed various studies. For example in PNAS 95, 10229-10234, 1998 (which was published after the earlier priority date of the present application) studies acute and chronic kainate excitotoxic damage to the optic nerve are reported.

The present invention will now be described by way of example only, with reference to the accompanying drawings, wherein:

5 **FIGURE 1** shows that the AMPA receptor antagonist NBQX reduces severity of paralysis during EAE in rats. NBQX (30mg/kg i.p. twice daily; 10-16 dpi) significantly reduces the peak disease score. Data represent the mean \pm SEM of disease score (n=10/group).

10 **FIGURE 2** shows that NBQX (30mg/kg i.p. twice daily; 10-16 dpi) reduces weight loss during the course of EAE in rats prior to cessation of treatment (16 dpi). Data represent the mean \pm SEM of disease score (n=10/group).

15 **FIGURE 3** shows that the non-competitive AMPA antagonist GYKI53773 reduces the severity of paralysis during EAE. GYKI53773 (30mg/kg i.p. twice daily; 10-16 dpi) significantly reduces the peak disease score. Data represents the mean \pm sem of disease score, standardised to days after disease onset (\bullet Vehicle n=9; \circ GYKI53773 n=10).

20 **FIGURE 4** shows that the AMPA receptor antagonist NBQX reduces the severity of paralysis during chronic EAE. In A, NBQX, 30mg/kg (\circ ; n=10) and vehicle (\bullet ; n=9) were administered i.p. twice daily for 7 days starting on day 10 post immunisation (10-16 dpi; stippled bar). In B, NBQX, 30mg/kg kg (\circ ; n=7) and vehicle (\bullet ; n=10) were administered i.p. once daily for 17 days commenced on dpi 26 (26-42 dpi; hatched bar). Data represents the mean \pm sem of disease score.

25

FIGURE 5 shows that the AMPA/kainate receptor antagonist MPQX reduces the severity of paralysis during EAE. MPQX (10mg/kg i.p. twice daily; 10-16 dpi) significantly reduces the peak disease score. Data represents the mean \pm sem of disease score, standardised to days after disease onset (\bullet Vehicle n=26; \circ MPQX n=12).

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5 **FIGURE 6** shows that the non-competitive AMPA antagonist GYKI52466 reduces the severity of paralysis during EAE. GYKI52466 (30mg/kg i.p. twice daily; 10-16 dpi) significantly reduces the peak disease score. Data represents the mean \pm sem of disease score, standardised to days after disease onset (● Vehicle n=15; ○ GYKI52466 n=16).

10 **FIGURE 7** shows that the non-competitive AMPA antagonist BIIR561 reduces the severity of paralysis during EAE. BIIR561 (30mg/kg i.p. twice daily; 10-16 dpi) significantly reduces the peak disease score. Data represents the mean \pm sem of disease score, standardised to days after disease onset (● Vehicle n=15; ○ BIIR561 n=16).

15 **FIGURE 8** shows that the non-competitive AMPA antagonist CP465022 reduces the severity of paralysis during EAE. CP465022 (10mg/kg i.p. twice daily; 10-16 dpi) significantly reduces the peak disease score. Data represents the mean \pm sem of disease score, standardised to days after disease onset (● Vehicle n=9; ○ CP465022 n=9).

EXAMPLES

20 Experimental allergic encephalomyelitis (EAE), an inducible autoimmune disease, represents the best characterized animal model of a demyelinating disorder and drugs active in this model proved to be active in humans (Pender MP (1996). Experimental autoimmune encephalomyelitis, In Autoimmune Neurological Disease, Editors Pender MP and McCombe PA, Cambridge University Press. pp 26-88).

25 Here we describe a surprising observation on the reduction in neurological deficits during acute EAE in rats following treatment with a non-immunomodulatory and non-antiinflammatory agent, the AMPA receptor antagonists, 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo-(F)-quinoxaline (NBQX). Furthermore, the non-competitive AMPA antagonists
30 (-)-1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-4,5-dihydro-3-methylcarbamoyl-2,3-benzodiazepine (GYKI53773), 1-(4-aminophenyl)-4-methyl-

7,8-methylene-dioxy-5H-2,3-benzodiazepine (GYKI52466), 5-(2-[N,N-dimethylamino]oxy-phenyl)-3-phenyl-1,2,4-oxadiazol (BIIR561) and 3-(2-chlorophenyl)-2-[2-[6-[(diethylamino)methyl]-2-pyridinyl]ethenyl]-6-fluoro-4(3H)-quinazolinone (CP465022), and the AMPA/kainate receptor antagonist [1,2,3,4-tetrahydro-7-morpholinyl-2,3-dioxo-6-(trifluoromethyl)quinoxalin-1-yl]methylphosphonate (MPQX) reduced neurological deficits during acute EAE. In addition we also describe the reduction in neurological deficit during chronic EAE in mice following treatment with NBQX.

10 *Animals*

Female Lewis rats (205 ± 10 g) obtained from Charles River, Kent, UK, were housed in pairs under environmentally controlled conditions (6:00 a.m. - 6:00 p.m. light/dark cycle; 22-24°C; 45-55% humidity) and allowed free access to food and water. Experimental groups consisted of 10 animals. Female Biozzi mice (20±5g) obtained from Harlan, UK, were housed under the conditions described above. Experimental groups consisted of 7-10 animals.

Induction of Acute-Active EAE in Lewis Rats

Rats were immunised in each hind foot with 50 µl of inoculum containing 50 µg guinea pig myelin basic protein (MBP, prepared by the method of Dunkley and Carnegie (1974); final concentration 2 mg/ml), emulsified in Freund's complete adjuvant (CFA; Sigma, UK) containing Mycobacterium tuberculosis H37Ra (final concentration 5.5 mg/ml; Difco Laboratories, UK).

25 *Assessment of Clinical EAE in Lewis rats*

Animals were weighed and monitored daily and clinical disease scored as (0) no clinical signs; (1) flaccid tail and weight loss; (2) hind limb hypotonia with further weight loss; (3) complete hind limb paralysis; (4) paraplegia and (5) death. In addition, intermediate scores were assigned to animals which showed a loss of tonicity in the distal half of the tail (score = 0.5), paralysis of one hind limb (score = 2.5) or complete

Induction of chronic-active EAE in Biozzi mice

Assessment of Clinical EAE in Biozzi mice

NBQX administration regime

NBQX was initially dissolved in NaOH and diluted with water. pH was adjusted with HCl. Rats were injected i.p. twice daily (9 a.m. and 5 p.m.) on days 10 to 16 post immunisation with either vehicle or NBQX in the dose of 30mg/kg. Mice were injected i.p. either twice daily (9 a.m. and 5 p.m.) on days 10 to 16 post immunisation

or once daily (9 a.m.) on days 26 to 42 post immunisation with either vehicle or NBQX in the dose of 30mg/kg.

GYKI53773 administration regime

- 5 GYKI53773 was suspended in 5% cremophore in saline. Rats were injected i.p. twice daily (9 a.m. and 5 p.m.) on days 10 to 16 post immunisation with either vehicle or GYKI53773 in the dose of 30mg/kg.

GYKI52466 administration regime

- 10 GYKI52466 was suspended in 5% cremophore in water. Rats were injected i.p. twice daily (9 a.m. and 5 p.m.) on days 10 to 16 post immunisation with either vehicle or GYKI52466 in the dose of 30mg/kg.

BIIR561 administration regime

- 15 BIIR561 was suspended in 5% cremophore in water. Rats were injected i.p. twice daily (9 a.m. and 5 p.m.) on days 10 to 16 post immunisation with either vehicle or BIIR561 in the dose of 30mg/kg.

CP465022 administration regime

- 20 CP465022 was suspended in 5% cremophore in water. Rats were injected i.p. twice daily (9 a.m. and 5 p.m.) on days 10 to 16 post immunisation with either vehicle or CP465022 in the dose of 10mg/kg.

MPQX administration regime

- 25 MPQX was initially dissolved in NaOH and diluted with water. pH was adjusted with HCl. Rats were injected i.p. twice daily (9 a.m. and 5 p.m.) on days 10 to 16 post immunisation with either vehicle or MPQX in the dose of 10mg/kg.

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Results

Effect of NBQX on disease progression during EAE in the Lewis rat

Following immunisation with MBP, neurological deficit developed in 10/10 vehicle treated animals, 8 of which displayed paralysis of one or both hind limbs; the mean disease onset and duration were 11.8 dpi and 4.7 dpi respectively (Figure 1 and Table 1). Twice daily treatment from day 10 to 16 post immunisation with NBQX completely prevented the development of paralysis in 6 out of 10 rats, whilst one animal exhibited loss of tone in the most proximal part of the tail (score 0.25) for one day only. The remaining 3 rats displayed paresis of score 1, 2.5 and 3, the onset and duration of which were similar to vehicle injected animals. Thus NBQX significantly reduced disease duration ($p<0.001$), and peak and cumulative disease score ($p<0.01$) relative to vehicle treatment. NBQX also conferred protection on weight loss, significantly delaying the onset until 13 dpi ($p<0.01$) and decreasing the percent body weight lost at the cessation of NBQX administration (day 16; Figure 2 and Table 1).

Table 1. Parameters of disease activity during Lewis rat acute EAE

Treatment	Incidence (%)	^a Onset (d.p.i.)	Duration (days)	Peak Disease Score	^b Cumulative Disease Score	^c Weight Loss (%)
Vehicle	10/10 (100)	11.8 (11-14)	4.7 (4-5)	2.7 (2-3.25)	9.8 (5.5-13)	18 (12-23)
NBQX	4/10 (75)	11.8 (11-12)	1.5 (0-5)††	0.7 (0-3)†	2.4 (0-11.5)†	14 (5-20)*

Values in the table represent the mean and range where $n=10$; * $p<0.05$, $p<0.01$ and $p<0.001$ vs vehicle, Student t-test or Mann-Whitney U-test for parametric and non-parametric data respectively. a; $n=4$ for NBQX. b; Cumulative disease score calculated by summation of individual daily disease scores. c; Calculated as the weight on

cessation of treatment (16 dpi) expressed as a percent of the maximum weight before disease onset.

Effect of GYKI53773 on disease progression during EAE in the Lewis rat

- 5 Following immunisation with MBP, neurological deficit developed in 8/9 vehicle treated animals; the mean disease onset and duration were 11.9 dpi and 3.8 days respectively (Figure 3 and Table 2). Twice daily treatment from day 10 to 16 post immunisation with GYKI53773 significantly reduced disease duration ($p<0.05$) and peak and cumulative disease score ($p<0.01$) relative to vehicle treatment.

10

Table 2: Parameters of disease activity during Lewis rat acute EAE.

Treatment	Incidence (%)	^a Onset (d.p.i.)	Duration (days)	Peak Disease Score	^b Cumulative Disease Score	^c Weight Loss (%)
Vehicle	8/9 (89)	11.9 (10-16)	3.8 (0-5)	2.6 (0-3.5)	9.5 (0-14.75)	19 (7-26)
GYKI53773	6/10 (60)	12.7 (11-14)	1.9 (0-5)*	0.9 (0-2.25)†	2.1 (0-6)†	16 (11-20)

- 15 Values in the table represent the mean and range where $n=10$; * $p<0.05$, and † $p<0.01$ vs vehicle, Student t-test or Mann-Whitney U-test for parametric and non-parametric data respectively. a; $n=6$ for GYKI53773. b; Cumulative disease score calculated by summation of individual daily disease scores. c; Calculated as the weight on cessation of experiment (20 dpi) expressed as a percent of the maximum weight before disease onset.

20

Effect of NBQX on disease progression during chronic EAE in the Biozzi mouse

To determine whether AMPA receptor antagonists affect the clinical outcome of chronic EAE, NBQX was administered i.p. to immunised mice. Treatment with NBQX, 30mg/kg twice daily for 7 days starting on dpi 10, improved neurological

outcome reducing disease severity between dpi 10 to 48 [$F(1,38)=9.21$, $P<0.001$] (Fig. 4A). Treatment with NBQX, 30mg/kg once daily for 17 days commencing on dpi 26 also reduced disease severity between dpi 28 to 48 [$F(1,20)=2.76$, $P<0.05$] (Fig. 4B).

5 *Effect of MPQX on disease progression during EAE in the Lewis rat*

Following immunisation with MBP, neurological deficit developed in 26/26 vehicle treated animals; the mean disease onset and duration were 11.2 dpi and 4.8 days respectively (Figure 5 and Table 3). Twice daily treatment from day 10 to 16 post immunisation with MPQX significantly delayed disease onset ($p<0.05$), reduced disease duration ($p<0.001$) and peak and cumulative disease score ($p<0.001$) relative to vehicle treatment.

Table 3: Parameters of disease activity during Lewis rat acute EAE.

Treatment	Incidence (%)	^a Onset (d.p.i.)	Duration (days)	Peak Disease Score	^b Cumulative Disease Score	^c Weight Loss (%)
Vehicle	26/26 (100)	11.2 (10-13)	4.8 (3-6)	3.5 (2.5-4)	11.0 (8-14.5)	21 (15-28)
MPQX	7/12 (58)	12.3 (11-14)*	1.7 (0-5)††	1.2 (0-3)††	3.2 (0-11.5)††	22 (13-30)

15 Values in the table represent the mean and range where $n=10$; * $p<0.05$ and †† $p<0.001$ vs vehicle, Student t-test or Mann-Whitney U-test for parametric and non-parametric data respectively. a; $n=7$ for MPQX. b; Cumulative disease score calculated by summation of individual daily disease scores. c; Calculated as the weight on cessation of experiment (18 dpi) expressed as a percent of the maximum weight before disease onset.

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Effect of GYKI52466 on disease progression during EAE in the Lewis rat

Following immunisation with MBP, neurological deficit developed in 14/15 vehicle treated animals; the mean disease onset and duration were 11.4 dpi and 4.3 days respectively (Figure 6 and Table 4). Twice daily treatment from day 10 to 16 post immunisation with GYKI52466 significantly reduced peak and cumulative disease score ($p<0.01$) relative to vehicle treatment.

Table 4: Parameters of disease activity during Lewis rat acute EAE.

Treatment	Incidence (%)	^a Onset (d.p.i.)	Duration (days)	Peak Disease Score	^b Cumulative Disease Score	^c Weight Loss (%)
Vehicle	14/15 (93)	11.4 (10-16)	4.3 (0-6)	2.8 (0-3.5)	10.9 (0-14.75)	20 (7-26)
GYKI52466	15/16 (60)	11.6 (10-13)	4.0 (0.6)	2.4 (0-3.0)**	8.0 (0-13.75)**	20 (8-26)

Values in the table represent the mean and range where $n=10$; ** $p<0.01$ vs vehicle, Mann-Whitney U-test for non-parametric data. a; $n=15$ for GYKI2466. b; Cumulative disease score calculated by summation of individual daily disease scores. c; Calculated as the weight on cessation of experiment expressed as a percent of the maximum weight before disease onset.

Effect of BIIR561 on disease progression during EAE in the Lewis rat

Following immunisation with MBP, neurological deficit developed in 14/15 vehicle treated animals; the mean disease onset and duration were 11.4 dpi and 4.3 days respectively (Figure 7 and Table 5). Twice daily treatment from day 10 to 16 post immunisation with BIIR561 significantly reduced peak ($p<0.05$) and cumulative disease score ($p<0.001$) relative to vehicle treatment.

Table 5: Parameters of disease activity during Lewis rat acute EAE.

Treatment	Incidence (%)	^a Onset (d.p.i.)	Duration (days)	Peak Disease Score	^b Cumulative Disease Score	^c Weight Loss (%)
Vehicle	14/15 (93)	11.4 (10-16)	4.3 (0-6)	3.5 (0-3.5)	10.9 (0-14.75)	20 (7-26)
BIIR561	16/16 (100)	12.4 (11-19)	3.9 (1-5) ††	2.6 (0.5-3.25)*	7.8 (0.5-11.5) †	17 (5-23)*

Values in the table represent the mean and range where n=10; *p<0.05 and †p<0.001 vs vehicle, Student t-test or Mann-Whitney U-test for parametric and non-parametric data respectively. a; n=16 for BIIR561. b; Cumulative disease score calculated by summation of individual daily disease scores. c; Calculated as the weight on cessation of experiment expressed as a percent of the maximum weight before disease onset.

Effect of CP465022 on disease progression during EAE in the Lewis rat

Following immunisation with MBP, neurological deficit developed in 9/9 vehicle treated animals; the mean disease onset and duration were 10.6 dpi and 5.1 days respectively (Figure 8 and Table 6). Twice daily treatment from day 10 to 16 post immunisation with CP465022 significantly delayed disease onset (p<0.01), reduced disease duration (p<0.05), peak and cumulative disease score (p<0.01) relative to vehicle treatment.

Table 6: Parameters of disease activity during Lewis rat acute EAE.

Treatment	Incidence (%)	^a Onset (d.p.i.)	Duration (days)	Peak Disease Score	^b Cumulative Disease Score	^c Weight Loss (%)
Vehicle	9/9 (100)	10.6 (10-16)	5.1 (4-6)	3.5 (3.0-3.5)	12.8 (11.75-14.25)	23 (18-26)
CP465022	8/9 (89)	13.4 (11-17)**	3.4 (0-5)*	2.0 (0-3.0)**	7.2 (0-13.5)**	20 (10-28)

Values in the table represent the mean and range where $n=10$; $*p<0.05$ and $**p<0.01$ vs vehicle, Student t-test and Mann-Whitney U-test for parametric and non-parametric data respectively. a; $n=8$ for CP465022. b; Cumulative disease score calculated by summation of individual daily disease scores. c; Calculated as the weight on cessation of experiment expressed as a percent of the maximum weight before disease onset.

General remarks

The foregoing description of the invention is merely illustrative thereof and it should therefore be appreciated that various variations and modifications can be made without departing from the spirit or scope of the invention as set forth in the accompanying claims.

Where preferred or optional features are described in connection with particular aspects of the present invention, they shall be deemed to apply *mutatis mutandis* to other aspects of the invention unless the context indicates otherwise.

All documents cited herein are hereby incorporated by reference, as are any citations referred to in said documents.